EARLY DETECTION OF CENTRAL NERVOUS SYSTEM INVOLVEMENT IN HYPOTHYROIDISM BY ELECTROPHYSIOLOGICAL STUDY

Dissertation submitted to

THE TAMILNADU Dr. M. G. R MEDICAL UNIVERSITY

In partial fulfillment of the

regulations for the award of the degree of

M.D. (PHYSIOLOGY)

BRANCH-V

THANJAVUR MEDICAL COLLEGE AND HOSPITAL

THE TAMIL NADU Dr. M.G.R MEDICAL UNIVERSITY

CHENNAI, INDIA

APRIL 2013

CERTIFICATE

This is to certify that this dissertation entitled **'EARLY DETECTION OF CENTRAL NERVOUS SYSTEM INVOLVEMENT IN HYPOTHYROIDISM BY ELECTROPHYSIOLOGICAL STUDY'** is a bonafide work done by Dr.M.Jayanthi, under my guidance and supervision in the department of Physiology, Thanjavur medical college, Thanjavur during her post graduate course from 2010 to 2013.

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DECLARATION

I solemnly declare that this dissertation **"EARLY DETECTION OF CENTRAL NERVOUS SYSTEM INVOLVEMENT IN HYPOTHYROIDISM BY ELECTROPHYSIOLOGICAL STUDY"** was done by me in the Department of Physiology, Thanjavur Medical College and Hospital, Thanjavur under the guidance and supervision of my Professor Dr.R.VINODHA, M.D., Department of Physiology, Thanjavur Medical College, Thanjavur between 2010 and 2013.

This dissertation is submitted to the Tamilnadu Dr. M.G.R Medical University, Chennai in partial fulfilment of University requirements for the award of M.D Degree (Branch – V) in Physiology.

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ACKNOWLEDGEMENT

I express my sincere gratitude and thanks to my Professor & Head of Department Dr.R.VINODHA,MD, Thanjavur Medical College, Thanjavur for the constant unfathomable guidance, immense support, constructive suggestions and for being a great source of inspiration throughout the period of study.

I would like to thank the Dean, Thanjavur Medical College, Thanjavur, for granting me permission to conduct this research study at Thanjavur Medical College Hospital, Thanjavur.

I sincerely thank Head of Department of Medicine for permitting me to carry out the study in the outpatient department of Medicine.

I sincerely thank Head of Department of Surgery for permitting me to carry out the study in the outpatient department of Surgery.

I also thank Head of Department of Biochemistry for permitting me to carry out the biochemical evaluations in their department.

I express my thanks and gratitude to all my patients who co operated to undergo the study.

CONTENTS

INTRODUCTION

INTRODUCTION

Hypothyroidism is one of the most common endocrine disorders, affecting over one percent of the general population and about 5 percent of individuals over age of 60 years [1, 2]. It is a syndrome characterised by the clinical and biochemical manifestation of thyroid hormone deficiency in the target tissue [3]. Iodine deficiency remains the most common cause of hypothyroidism worldwide. In areas of iodine sufficiency, autoimmune disease (Hashimotos thyroiditis) and iatrogenic causes (treatment for hypothyroidism) are most common [4].

Thyroid hormone is essential for early brain development and play a key role in later brain functioning. It is involved in fundamental neurologic processes such as neurogenesis, axon and dendritic formation, neuronal migration, and synaptogenesis, with the timing of need for thyroid hormone varying among different brain structures. Structures showing the greatest need for thyroid hormone are the thalamus, cerebellum, caudate nucleus, hippocampus, cerebral cortex. In addition, thyroid hormone is involved in cochlear and retinal development. Thyroid hormone act by regulating specific brain genes and this thyroid specific gene regulation is accomplished via a set of distinct thyroid hormone receptors; the receptor distribution varies ontologically and regionally, with some brain structures showing a great need for thyroid hormone than others. This finding is significant for humans, in whom impairment from early thyroid hormone loss is more likely to

result in specific than global deficits; the exact nature will depend on the precise timing of thyroid hormone insufficiency [5].

Thyroid hormone deficiency is associated with peripheral and central nervous system dysfunction. The Central nervous system manifestations include slowing of all intellectual functions, lethargy, somnolence, loss of initiative, memory defects, depression and rarely convulsions and coma. [6]

The metabolic abnormalities decreased cerebral blood flow or abnormal depositions of mucopolysaccharride that usually accompany hypothyroidism are believed to cause these symptoms [7].These CNS manifestations are largely reversible with treatment [8].

Involvement of central nervous system in overt hypothyroidism has previously been shown by (Ladenson et al, Kedhr et al) on the basis of visual evoked potential in adult patients and of BAEPS (A.R.D.thornton, S.J.Jarvis) and SSEPS in infants and adults (Bongers –Schokking et al, Ozkardes et al) [7, 9-12].

In our country, a large number of patients are suffering from thyroid deficiency which varies from mild to severe form. As most of the patients are illiterate and of low socio economic status, they were not aware about consequences as well as the complication of delayed or irregular treatment. Evoked potentials are particularly suited for a non invasive evaluation of a number of afferent pathways in the nervous system [11].

Hence the electrophysiological study was done in hypothyroid patients, even in the asymptomatic ones, early in the course of disease in order to detect the nervous system involvement.

AIM & OBJECTIVES

AIM AND OBJECTIVES

- This study was undertaken to compare electrophysiological parameters between hypothyroid patients and control.

- To evaluate functional changes in nervous system in hypothyroidism by different electrophysiological parameters like visual evoked potential, Brain stem auditory evoked potential, Somatosensory evoked potential.

REVIEW OF LITERATURE

REVIEW & LITERATURE

THYROID GLAND:

The thyroid gland was first described by Galen [130-210 AD] in his work "De voce". The gland was named thyroid by Thomas Whorton (1614-1673) because of its proximity to the thyroid cartilage. Despite its name (thyreos in Greek means "shield", and "schilddruse" in German means "shield gland"). The active principle of the thyroid extract was isolated by Kendall on Christmas day 1914 and named thyroxine [13].

EPIDEMIOLOGY:

Thyroid disease is common, particularly in women, with prevalence in community of 3-5% [14]. Primary hypothyroidism is a common disease worldwide, especially in iodine deficient area. It accounts for approximately 99% of case, with less than 1% being due to Thyrotropin (TSH) deficiency known as central or secondary hypothyroidism [15]. Hashimoto's thyroiditis / chronic lymphocytic thyroiditis is the commonest cause of goitrous hypothyroidism in iodine sufficient parts of the world. It is predominantly a disease of women, with a female to male ratio of 5:1 [16]. The mean annual incidence rate of autoimmune hypothyroidism is up to 4 per 1000 women and 1per 1000 men [4].

FUNCTIONAL ANATOMY OF THYROID GLAND:

The thyroid is one of the largest endocrine organs, weighing approximately 20gms.The thyroid gland is made up of two lobes of endocrine tissue joined in the middle by a narrow band of tissue, the isthmus, and giving it a bow tie shaped appearance and is located on either side of trachea just below the larynx. Each lobe of thyroid gland is divided into various lobules by fibrous tissue septa. Each lobule is made up of an aggregation of several follicles. Follicle is the functional unit of thyroid gland.

Thyroglobulin is considered as the chief substances of the colloid, which is found to be a large complex molecule. Thyroid hormones are incorporated within them in various stages. Thyroxine (T_4) and triiodothyronine (T_3) are derived from the amino acid tyrosine, which are produced by follicular cells.

SYNTHESIS AND STORAGE OF THYROID HORMONE:

Tyrosine and iodine are the basic ingredients for thyroid hormone synthesis. Both of which must be taken up from the blood by the follicular cells. All the steps of thyroid hormone synthesis occur on the large thyroglobulin molecule, which subsequently store the hormones. The steps involved in the synthesis of thyroid hormones are:

a.) **Iodine Trapping:** The first step in the synthesis of thyroid hormones is uptake of iodide by thyroid gland which occurs against the electrochemical gradients by a

sodium iodide co transport /symport system or iodine pump that is located in the outer membranes of the follicular cells. Almost of all of the iodine in the body is moved against its concentration gradient to become trapped in the thyroid for the purpose of thyroid synthesis.

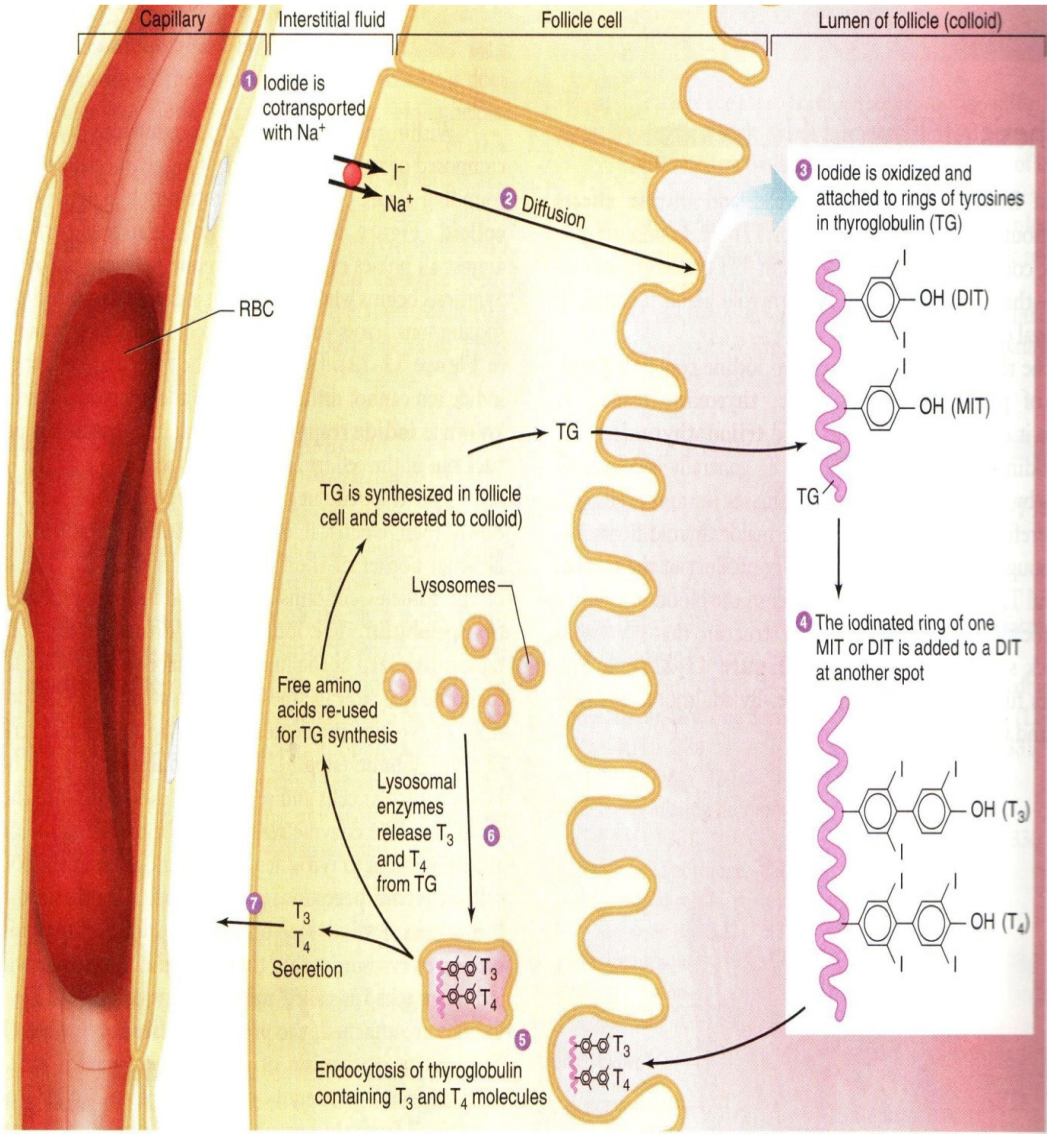


Fig: 1 steps in synthesis and release of thyroid hormones

b.) **Synthesis and secretion of thyroglobulin:** Thyroglobulin is a large glycoprotein that is synthesized on the rough endoplasmic reticulum of thyroid

follicular cells as peptide unit of molecular weight 3, 30,000. These units combine into a dimer, after which carbohydrate moieties are added as the molecule moves to the Golgi apparatus. The completed glycoprotein is contained in small vesicles, which move to the apical plasma membrane and release into the lumen of follicle. Each molecule of thyroglobulin contains about 123 tyrosine residues which can serve as substrate for the formation of thyroid hormones.

c.) **Oxidation of iodide:** Once within the gland, iodide rapidly moves to the apical surface of the follicular cells. From these, it is transported into the lumen of the follicles by a sodium independent iodide/chloride transporter called Pendrin. The iodide is then immediately oxidised to iodine by the enzyme peroxidase present near the apical border of the follicular cells. The immediate oxidant for this reaction is hydrogen peroxidase which is supplied by an NADPH dependent system.

d.) **Organification of thyroglobulin:** Within the colloid, iodine is quickly attached to a tyrosine within the thyroglobulin molecule and this refers to iodination of tyrosine residue. Tyrosine of thyroglobulin is first iodinated at position 3 to form monoiodotyrosine (MIT) and then at position 5 to form diiodotyrosine (i.e.) attachment of one iodine to tyrosine yields monoiodotyrosine, attachment of two iodines to tyrosine yields diiodotyrosine respectively. This reaction occurs at the apical membrane of the cell as soon as thyroglobulin molecule is released by the secretory granules by exocytosis and requires thyroid peroxidase.

e.) **Coupling reaction:** The process of iodination of tyrosine residues is followed by coupling reaction, which lasts for few minutes to hour. Coupling of two DITs

(each bearing two iodine atoms) yields tetraiodothyronine (T_4) the iodine form of thyroid hormone. Coupling of one MIT (with one iodine) and one DIT (with two iodines) yields triiodothyronine (T_3).Coupling does not occurs between two MIT molecules. The enzyme peroxidase is required during coupling.

f.) **Storage:** Once thyroglobulin has been iodinated is stored in the lumen of the follicle as colloid until they are split off and secreted. It is estimated that the stored thyroid hormones can meet the body requirements for 1-3 months.

SECRETION OF THYROID HORMONE:

Once thyroglobulin has been iodinated, it is stored in the lumen of the follicle as colloid. Release of Thyroxine and Triiodothyronine into the blood stream requires binding of thyroglobulin to the receptor megalin, followed by endocytosis and lysosomal degradation of thyroglobulin. Enzymatically released Thyroxine and Triiodothyronine then leaves the basal side of the cell and enters the blood. The MIT and DIT are rapidly deiodinated within the follicular cells by the enzyme deiodinase. In this way iodide is retrieved for recycling along with the tyrosine into T_4 and T_3 synthesis [17].

CHARACTERISTIC OF CIRCULATING TRIIODOTHYRONINE (T_3) & THYROXINE (T_4):

Hormone property	**T_3**	**T_4**
Concentration of total hormone	0.14µg/dl	8µg/dl
Fraction of total hormone in the free Form	0.3%	0.02%
Free (unbound form)	6×10^{-12} M	21×10^{-12} M
Fraction directly from the thyroid	20 %	100%
Serum half life	0.75 days	7 days
Intra cellular hormone fraction	70%	20%
Relative metabolic potency	1	0.3
Production rate, including Peripheral conversion	32µg/d	90µg/d
Receptor binding	10^{-11} M	10^{-10} M

REGULATION OF THYROID HORMONE FUNCTION & SYNTHESIS:

The large intra-glandular store of hormone buffers the effect of acute increase or decreases in hormone synthesis. Autoregulatory mechanism within the gland in turn tend to maintain the constancy of the thyroid hormone pool. Finally the classic feedback mechanism sense variation in the availability of thyroid hormones and their metabolic impact at the periphery.

HYPOTHALAMIC-PITUITARY-THYROID AXIS SYSTEM:

The Hypothalamic-pituitary-thyroid axis is a classic example of an endocrine feedback loop. Hypothalamic thyrotropin releasing hormone (TRH) stimulates production of thyroid stimulating hormone (TSH) by pituitary gland, which in turn, stimulates thyroid hormone synthesis and secretion [4].

PHYSIOLOGICAL ACTIONS OF THYROID HORMONES:

Thyroid hormone is the primary determinant of the body's overall metabolic rate and is also important for bodily growth and normal development and function of the nervous system.

EFFECT ON BASAL METABOLIC RATE:

Thyroid hormone in general increases the body's overall basal metabolic activities. They are calorigenic and hence, increase oxygen consumption and heat production [18]. The basal metabolic rate can increase by 60 percent to 100 percent above normal when large amount of T_4 are present [16].

CALORIGENIC EFFECT:

Increased metabolic activity results in increased heat production. Thermogenesis must also increase concomitantly with oxygen use [19].

Thyroid hormones increase membrane Na^+ k^+ adenosine triphosphatase (ATPase) concentration and activity and increase membrane Na^+ and K^+ permeability. As much as 15% to 40% of the basal energy used in the cell is applied to maintaining this electrochemical gradient. Thyroid hormone increases the activity of Na^+ K^+ ATPase and hence, increases energy expenditure in resting cells. It increases energy expenditure by increasing futile cycling because they frequently stimulate both anabolic and catabolic enzymes of the same pathway [18].

EFFECT ON NERVOUS SYSTEM:

Thyroid hormone regulates the timing and pace of development of the central nervous system [19]. They regulate neuronal proliferation, and differentiation, myelinogenesis, neuronal outgrowth, and synapse formation [18]. Thyroid hormone acts by regulating specific brain gene, which underlie the basic processes of brain development. Thyroid specific gene regulation is accomplished via a set of distinct thyroid hormone receptors, which along with specific coactivators and corepressors activate or deactivate particular brain genes. It also plays an important role in neurotransmission [5].

During early life, thyroid hormone controls production of neurotransmitters, whereas in later life, thyroid hormone regulates catecholamine production and responsiveness. In addition, thyroid hormone a.) Activates neurones via astrocytes, b.) Affects synaptic transmission between neurons through release of glutamate, c.) Up regulates sodium – dependent neurotransmitter transporter gene and other genes involved in neurotransmitter function, and d.) Control GABA release and reuptake, as well as GABA receptor function. Furthermore, thyroid hormone effects on neurotransmitter function are different in the developing brain than in adult brain. Because these actions have functional implications for humans, they underscore the need to maintain proper levels of thyroid hormone beyond the period of early brain growth. [4]

Thyroid hormone also enhances alertness, wakefulness, and learning capacity, auditory sense, and awareness of hunger, memory, and responsiveness to various stimuli. Furthermore, the speed and amplitude of peripheral nerve reflexes are increased by thyroid hormone [19].

HYPOTHYROIDISM:

Reduced production of thyroid hormone by the thyroid gland results in the clinical state termed hypothyroidism. It may be primary or secondary.

Hypothyroidism as a clinical syndrome was described in 1874 by Gull under the name of myxedema in view of the swollen skin (edema) and its excessive content of mucin [3].

PRIMARY HYPOTHYROIDISM:

Primary hypothyroidism refers to thyroid hormone deficiency caused by intrinsic deficiency (i.e. permanent loss or destruction of the thyroid, through processes such as autoimmune destruction or irradiation injury) of the thyroid gland that affects the synthesis and secretion of T_4 and T_3 [20].

SECONDARY HYPOTHYROIDISM:

Secondary hypothyroidism refers to insufficient stimulation of a thyroid gland, as the result of hypothalamic or pituitary disease or defects in the TSH molecule [15].

ETIOLOGY:

The causes of hypothyroidism vary, depending on whether the disease is primary or secondary.

CAUSES OF HYPOTHYROIDISM

Primary hypothyroidism:

Autoimmune Hypothyroidism:		Hashimotos thyroiditis Atrophic thyroiditis.
Iatrogenic	:	^{131} I treatment, Subtotal or Total thyroidectomy, Therapeutic irradiation for Non thyroidal malignancy.
Congenital Hypothyroidism	:	Thyroid agenesis or dysplasia,

		Dyshormonogenesis,
		TSH receptor defects,
		Iodine deficiency,
		Idiopathic TSH unresponsiveness.
Drugs	:	Iodide, Lithium, antithyroid dugs,
		Sulfonamides, and ethionamide,
		Cytokines(interferon-α,interleukin-2)
		aminoglutethimide.
Thyroid Infiltration	:	Amyloidosis, sarcoidosis,
		Hemochromatosis, scleroderma, cystinosis,
		Riedels Struma, over expression of type III
		Deiodinase in infantile haemangioma.

Secondary Hyperthyroidism:

Acquired:

Hypopitutarism	:	Tumors, Sheehan's syndrome
		Pituitary Surgery,
		Irradiation,
		Infiltrative disorders,

Trauma,

Genetic forms of combined pituitary hormone deficiencies.

Hypothalamic Diseases : Tumours,

Trauma,

Infiltrative Disorders,

Idiopathic.

Bexarotene treatment

(Retinoid X receptor agonist).

Congenital:

TSH deficiency or structural abnormality

TSH receptor defect

Transient Hypothyroidism:

- Subacute thyroiditis,

- Silent thyroiditis, including postpartum thyroiditis,

- After ^{131}I treatment or subtotal thyroidectomy for Graves disease.

- Withdrawal of thyroxine treatment in individuals with an infarct thyroid.

PATHOGENESIS:

Clinical hypothyroidism shows deficiency of thyroid hormones and their action at the target tissue level. Binding of T_3 to the receptor complex which in turn bind to thyroid receptor elements are located on certain genes over the regulatory regions. Based on the variation it shows response to thyroid hormones. The effect of hypothyroidism can be best studied on the basis of specific deficiency of molecular action [21].

Autoimmune thyroiditis is characterised by thyroid cell apoptosis leading to follicular destruction rather than thyroid stimulation and thyroid cell hyperplasia. Although both auto antibodies to thyroid peroxidase and thyroglobulin may be complement-fixing and cytotoxic, the thyroid gland is infiltrated by both B cells and T cells; the latter are armed with Fas ligand and capable of destroying thyroid cells expressing Fas via apoptosis [15].

CLINICAL MAINFESTATIONS OF HYPOTHYROIDISM:

Hypothyroidism can affect all organ systems of the body, and these manifestations are largely depends on the degree of hormone deficiency.

Symptoms:

Fatigue

Lethargy

Sleepiness

Depression

Cold intolerance

Hoarseness

Dryness of skin

Decreased perspiration

Weight gain

Decreased appetite

Constipation

Menstrual irregularities

Joint pain

Paresthesia

Signs:

Slow speech

Slow movements

Bradycardia

Non pitting edema

Hyporeflexia

Delayed relaxation of reflexes

Symptoms and signs associated with specific causes of hypothyroidism:

Diffuse or nodular goiter

Symptoms and signs of pituitary or hypothalamic tumor

Visual impairment, Headache [8]

EFFECTS OF HYPOTHYROIDISM IN BRAIN:

In hypothyroidism, Neurological complications are more common and all levels of the nervous system may be involved. Hormonal alterations and immune mechanisms are the possible explanations for the neurological complications in hypothyroidism [22].

The neurologic manifestations of acquired hypothyroidism in chidren and adults are varied [8] and include mental changes, seizures, dementia, cerebellar ataxia, cranial nerve disorders, sleep apnea and coma.

MENTAL DYSFUNCTION:

Mental and psychological dysfunction is relatively common in untreated hypothyroidism. All intellectual functions, including speech, are slowed in thyroid

hormone deficiency. Loss of initiative is present, slow wittedness and memory defects are also common, lethargy and somnolence are prominent, and dementia in elderly patients may be mistaken for senile dementia. Headaches are frequent. Psychiatric disorders are common and are usually of the paranoid or depressive type and may induce agitation (myxedema madness) [15].

SEZIURE:

About 20 percent of patients with untreated hypothyroidism will develop seizures or syncopal episodes. Cerebral hypoxia due to circulatory alterations may predispose to confusional attacks and syncope. Drop attacks also occur as a complication of hypothyroidism that resolves with hormone replacement therapy [22].

CEREBELLAR ATAXIA:

Acquired cerebellar ataxia has been described in patients with hypothyroidism. Unsteadiness of gait may be found in the earliest clinical descriptions of hypothyroidism. Some patients describe clumsiness or unsteadiness of gait, but they have no nystagmus or other signs of cerebellar dysfunction.

The rapid resolution of the ataxia with hormone replacement therapy in most patients suggests that the problem may be caused by a reversible metabolic factor [22].

CRANIAL NERVE DISORDERS:

Hearing loss: Deafness is a very characteristic and troublesome symptom in hypothyroidism [23]. About 25% of hypothyroid patients have substantial hearing loss. Both nerve and conduction deafness and combination of the two have been reported.

Two-thirds of patients complain of dizziness, vertigo, or tinnitus occasionally, these problems again suggest damage to the cochlear nerve or labyrinth, or possibly to the cerebellum. Whatever type of deafness is present, there is marked improvement after thyroid hormone therapy [23].

Endemic cretinism is a congenital type of thyroid deficiency in humans. It has been associated with deformities of the malleus and incus, incomplete ossification of the stapes, distortions of the round and oval windows, poorly developed mastoid processes, thickened middle ear mucosa, and hyperostosis of the promontory, and even with occasional closure of the round window.

Acquired hypothyroidism may follow drug treatment, surgery, or irradiation. It may also result from infections or dietary lack of iodine. 25 to 50% of these patients develop hearing loss that is occasionally reversible with thyroid hormone treatment. The level of hearing loss correlates somewhat with the severity of the thyroid hormone deficiency [24].

Visual deficit: In longstanding primary hypothyroidism, hyperplasia of the thyrotrope may cause pituitary gland enlargement. Pressure effect of enlarged pituitary on the optic chiasma results in subtle visual field defects in more number

of patients with primary hypothyroidism [8]. Visual evoked potentials may be delayed as a consequence of abnormal cerebral cortical metabolism [23]. Thyroid hormone replacement therapy may lead to a reduction in pituitary size and an improvement in vision.

DISORDERS OF SLEEP:

Disturbances of sleep are common in patients with hypothyroidism. Many of the hypothyroid patients have evidences of upper airway obstruction resulting from deposition of mucopolysaccharides and extravasation of protein into the tissues of the tongue and nasopharynx, as well as hypertrophy of the genioglossus and leading obstructive sleep apnea. In other patients, the sleep apnea seems to be central in origin. Disturbance in serotonin neurotransmission may be the mechanism involved in central apnea of hypothyroidism [22].

ENCEPHALOPATHY AND COMA:

Occasionally, a life-threatening encephalopathy known as myxedema coma may result from a variety of precipitating factors causing decompensation of the physiological adaptations to hypothyroid state [22].

Clinical features are universally present in myxedema coma are defective temperature control, depression of level of consciousness and a precipitating illness or event. The pathophysiology of myxedema coma involves three major aspects: a)

carbon dioxide retention and hypoxia, b) fluid and electrolyte imbalance c) hypothermia. [16]

HASHIMOTO'S ENCEPHALOPATHY:

Hashimoto's encephalopathy is a term that has been applied to patients with chronic autoimmune thyroiditis who have confusion, delirium, dementia, tremor, myoclonus, ataxia, focal or generalized seizures, and occasionally stroke-like episodes. There is a preponderance of female patients. Nearly all patients have had high serum concentrations of antithyroid peroxidase or other antithyroid antibodies. The encephalopathy usually well responds to gulcocorticoids [8].

PERIPHERAL NEUROPATHY IN HYPOTHYROIDISM:

Neurologic complications, including polyneuropathy, are well-known finding in overt hypothyroidism, with a prevalence ranging from 42% to 72% [25]. Peripheral neuropathy may be a manifestation of hypothyroidism which usually develops insidiously over a long period of time due to irregular intake of drugs or lack of thyroid hormone replacement. Both entrapment mononeuropathies and diffuse neuropathy are the complication of hypothyroidism [22].

ENTRAPMENT NEUROPATHY:

Entrapment neuropathy, most commonly affecting the median nerve (carpal tunnel syndrome), is perhaps the most common discrete neurologic abnormality in adult

hypothyroidism [9]. Less common is a sensory or sensorimotor neuropathy, for which evidence implicates both segmental demyelination and axonal degeneration [26]. Deposition of acid mucopolysaccharides in the nerve and surrounding tissues leads compression of median nerve [8].

DIFFUSE PERIPHERAL NEUROPATHY:

The peripheral neuropathy is usually relatively mild and predominantly sensory. The severity of the neuropathy appears to correlate with the duration of the disease rather than the severity of the biochemical abnormalities. Numbness and tingling of the extremities are frequent. The tendon reflexes are slow, especially during the relaxation phase, producing the characteristic “hung-up reflexes”; the phenomenon is due to a decrease in the rate of muscle contraction and relaxation rather than a delay in nerve conduction [15].

HYPOTHYROID MYOPATHY:

The major clinical features of hypothyroid myopathy include muscle pain, weakness, cramps, sluggish movements and reflexes, and myoedema (ridging of the muscle on percussion), increase in muscle bulk. Rhabdomyolysis and weakness of respiratory muscles are rarely reported [27].

Kocher-Debre-Semelaigne syndrome is the unusual association of muscle hypertrophy in childhood hypothyroidism [28]. Stiffness and aching of muscles are common. Delayed muscle contraction and relaxation cause the slowness of movement and delayed tendon jerk. Myoclonus may be present [15].

EXAMINATION OF PATIENT:

Physical examination:

Examination of thyroid gland: The thyroid can be best palpated with both hands from behind the patient. Each lobe of the thyroid can be palpated by standing in front of the patient using the thumbs. In addition to the examination of the thyroid gland itself, the physical examination should include a search for signs of abnormal thyroid function and the extrathyroidal features of ophthalmopathy and dermatopathy.

LABORATORY EVALUATION:

Hormone assay:

These tests are considered best and are widely used for the diagnosis of various thyroid disorders. An accurate estimation of thyroid hormones can be done by Radioimmunoassay (RIA) or by ELISA method.

Increased sensitivity and specificity of thyrotropin assays have greatly improved laboratory assessment of thyroid function. Because thyrotropin levels change dramatically in response to alterations of circulating Thyroxine or Triiodothyronine levels, a logical approach to thyroid testing is to first determine whether TSH is suppressed, normal or elevated.

The finding of an abnormal TSH level must be followed by measurement of circulating thyroid hormone levels to confirm the diagnosis of hypothyroidism (in which thyrotropin elevated) or hyperthyroidism (Thyrotropin suppressed).

Measurement of total T_3, T_4 and free T_3, T_4 are done to confirm the diagnosis of thyroid diseases.

Normal values of thyroxine: [29]

AGE	MALES		FEMALES	
	SI unit nmol	µg/dl	SI unit nmol	µg/dl
15-60 yrs	59-135	4.6-10.5	65-138	5.5-11
>60yrs	65-138	5-10.7	65-138	5-10.7

Normal values of Triiodothyronine: [29]

AGE	MALES		FEMALES	
	SI units	ng/dl	SI units	ng/dl
16-20yrs	1.23-3.23	80-120	1.23-3.23	80-120
20-50yrs	1.08-4.14	70-204	1.08-4.14	70-204
50-90yrs	0.62-2.79	40-181	0.62-2.79	40-181

Normal values of thyrotropin: [29]

AGE	MALES	FEMALES
	SI units	SI units
21wks-20yrs	0.7-64	0.7-64
21-54yrs	0.4-4.2	0.4-4.2
55-87yrs	0.5-8.9	0.5-8.9

TEST TO DETERMINE THE ETIOLOGY OF THYROID DYSFUNCTION:

Detection of antithyroid antibodies is useful in diagnosing autoimmune thyroid disorders. The presence of thyroid peroxidase (TPO) antibodies indicating the cause of hypothyroidism is autoimmune. On the other side, the absence of TPO antibodies requires a search for less common cause of hypothyroidism such as transient hypothyroidism, infiltrative thyroid disorders, and external irradiation.

RADIOACTIVE IODINE UPTAKE:

Measurement of radioactive iodine uptake (RAIU) is rarely needed in the evaluation of hypothyroidism. The RAIU may be normal or even increased when hypothyroidism results primarily from a biochemical defect in thyroid hormone synthesis rather than thyroid cell destruction leading to compensatory thyroid enlargement [15].

THYROID SCAN:

A radio nucleotide scan of thyroid using ^{123}I, ^{125}I, ^{131}I or ^{99m}Tc is useful in demonstrating functioning thyroid tissue. On isotope scanning, swellings are classified into hot (overactive) or cold (underactive). About 80% of discrete swelling are cold, but only 15% prove to be malignant.

FINE NEEDLE ASPIRATION CYTOLOGY:

Fine needle aspiration cytology is the investigation of choice in discrete thyroid swellings. Thyroid disorders that may be diagnosed by FNAC include colloid nodules, thyroiditis, papillary carcinoma, medullary carcinoma, anaplastic carcinoma and lymphoma [30].

ULTRASONOGRAPHY OF THYROID GLAND:

Ultrasonography is a non invasive technique allows evaluation of an enlarged thyroid gland. It gives information about the shape and dimension of discrete nodules of thyroid gland.

TEST FOR PERIPHERAL NEUROPATHY:

Clinical examination:

Physical examination of patients with suspected distal sensory, motor, or focal (i.e. entrapment or noncompressive) neuropathic symptoms should include assessments for peripheral neuropathy.

Clinical investigation included a set of screening questions referring to the principal symptoms of polyneuropathy (i.e. muscle cramps, restless legs syndrome, burning feet, muscle pain, problems with object handling and "glove and stocking" Paresthesia)

Testing for peripheral neuropathy begins with assessment of fine touch and pinprick sensation. Vibratory sense in the feet is tested with a 128-Hz tuning fork placed at the base of the great toe. Raffaello et al observed in their case reports of four hypothyroid patients, two of them had diminished touch, vibration and joint position sense [31].

Examination of deep tendon reflexes and muscle strength: With neuropathy, deep tendon reflexes are commonly hypoactive or absent. Ruurd F Duyff et al in their prospective study showed that 38% of the hypothyroid patients had weakness in one or more muscle groups and diminished ankle reflex [32].

Perform Tinel testing. Paresthesia and pain suggests median nerve injury. Perform cranial nerve testing. Have the patient walk on the heels and toes; heel-toe walking tests not only distal lower extremity strength but balance, as well.

NERVE CONDUCTION STUDIES:

The type and extent of nerve damage study can be analyzed using nerve conduction study. The parameters of motor nerve conduction study include the onset of latency, duration, and amplitude of compound muscle action potential (CMAP) and nerve

conduction velocity. The sensory nerve conduction can be measured orthodromically or antidromically. As like that of motor nerve conduction study, the sensory nerve conduction measurement includes onset latency, amplitude, duration of sensory nerve action potential (SNAP) and nerve conduction velocity.

The nerve conduction studies gives information about the involvement of axon, myelin, or both.

ELECTROMYOGRAPHY: (EMG)

Electromyography refers to recording of action potentials of muscle fibres firing singly or in groups near the needle electrode in a muscle. EMG changes help in objectively documenting the topography of disease process, such as focal versus generalized myopathy; or the neurogenic changes being restricted to nerve, plexus, root or segmental distribution; and duration of disease process, i.e. acute, subacute, and chronic.

ELECTROMYOGRAHY FINDINGS IN HYPOTHYROIDISM:

Electromyography reveals typical myopathic pattern with decreased amplitude and duration of motor unit potential as well as increase in polyphasia. Fasiculations, fibrillations, and sharp waves are uncommon in hypothyroid myopathy.

Nerve conduction studies and electromyography studies have an important role in the detection of peripheral neuropathy [33].

MUSCLE BIOPSY:

In hypothyroid myopathy, the muscle biopsy changes of type II muscle fiber atrophy usually parallel the degree of clinical wasting and weakness. Type I fiber hypertrophy has been described particularly in women. Isolated necrotic fibres are rarely seen in this condition. In severely affected muscles, intracellular glycogen deposits may be found in muscle fibers and there may be vacuoles as well. Non specific ultrastructure features include myofibrillar degeneration, Z – disc streaming, lipofuscin accumulation, and mitochondrial alterations. The weakness in hypothyroidism is due to a complex set of effects of thyroid hormone deficiency on skeletal muscle structure and function. Impaired muscle energy metabolism appears to be the primary factor. Hormone replacement therapy improves most of the muscular abnormalities.

NERVE CONDUCTION STUDY IN HYPOTHYROIDISM:

Findings on nerve conduction studies depend on the pattern of nerve damage. Khedr et al in their electrophysiological study in hypothyroid patients showed that 52% of patients had peripheral nervous system affection. 35% of patients had entrapment neuropathy followed by diffuse distal axonal neuropathy (9%) and myopathy (9%) [8].

Ettore Beghi et al conducted a nerve conduction study in hypothyroid patients, and found higher motor distal latencies with prolonged motor nerve conduction velocities for median, ulnar, sural, common peroneal nerves [34].

D.J. Dick et al performed nerve conduction studies in hypothyroid patients before and after the treatment with thyroxine and observed slowing of motor and sensory nerve conduction velocities and prolongation of distal latencies in median, ulnar, common peroneal, posterior tibial and sural nerve before treatment with thyroxine and reported all the nerve conduction velocities and latencies are returned to normal on treatment with thyroxine [35].

Yeasmin S et al has evaluated sensory neuropathy in hypothyroid patients. They found significantly prolonged sensory distal latencies with lower sensory nerve conduction velocities of median, ulnar, and sural nerve in their nerve conduction study and suggested that the thyroid hormones stimulate the mitochondrial respiratory activity to produce energy in form of ATP during aerobiosis under normal physiological condition. Hormones also increase the ATPase activity and consequently Na+/K+ pump activity cause subsequent alteration of pump dependent axonal transport and thereby may lead to peripheral neuropathy [36].

Fariba Eslamian et al has evaluated the electrophysiological changes in patients with overt hypothyroidism and their results are increases in median compound motor action potentials and sensory nerve action potentials (SNAPs) latencies and slowing of conduction as well as reduction in sural SNAPs amplitude. They reported 32.5% of carpal tunnel syndrome, 15% of neuropathy, and 7.5% of myopathy in patients with hypothyroidism [37].

INVESTIGATION FOR CENTRAL NERVOUS SYSTEM INVOLVEMENT IN HYPOTHYROIDISM:

MRI: Magnetic resonance imaging is non-invasive and uses magnetic fields and radio waves instead of ionizing radiation. Structural MRI methods allow creating images of anatomical structures in an excellent spatial resolution. Magnetization transfer is sensitive to myelin content and is therefore useful in detecting early demyelination process.

fMRI: Functional magnetic resonance imaging has become the tool of choice to study functional aspects of the human brain. fMRI in patients with thyroid disease of different duration and severity could help to identify functional aberrations such as memory impairments or altered emotional processing, which has long been suggested from animal studies.

PET (positron emission tomography) & **SPECT** (single photon emission computer tomography): Thyroid hormones are known to affect the vascular system. Hypothyroidism is associated with impaired fibrinolysis and blood coagulation resulting in cerebrovascular disease. It also compromises protective endothelial and thrombocyte functions as well as lipid metabolism.

PET & SPECT measurement of cerebral blood flow in hypothyroidism was associated with global, diffuse hypoperfusion. Several studies pointed to more regional effects including perfusion deficits pronounced in posterior brain region or in the parietal lobe [38].

ELECTROENCEPHALOGRAPHY: (EEG)

Electroencephalography is a non-invasive technique in which the brain's electrical activity is recorded from the scalp to evaluate the function of the brain.

An excess of low voltage slow activity has been reported in hypothyroid adult patients. The alpha blocking response may be poor or even absent [39]. The EEG is diffusely abnormal in Hashimoto's thyroiditis [26].

ELECTROPHYSIOLOGICAL STUDY IN HYPOTHYROIDISM:

Clinical electrophysiological examination and evaluation consist of the recording, analysis, and interpretation of biochemical activity of muscles and nerve in response to volitional activation or electrical stimulation.

Evoked potentials are voltage changes monitored from the electrically excitable tissue if the cerebral cortex, brainstem, and spinal cord in response to various applied sensory stimuli. The function of pathways leading to three different central nervous system sensory areas, the somatosensory cortex, the visual cortex, and the auditory region of the brainstem, can be evaluated using electro physiologic test [40].

Evoked potentials are frequently used to evaluate central nervous system physiology. Both electroencephalography (EEG) and evoked potentials (EPs) are used to measure the brain electrical activity. The EEG displays spontaneous brain activity as a continuous graph of voltage and frequency changes occurring over time. In contrast, EPs reflect activity of the central nervous system in response to specific stimuli [41].

Evoked potential recordings are useful in evaluating lesions in the afferent pathways under study. They assess the functional integrity of these pathways, whereas imaging techniques such as MRI and CT are useful in evaluating structural lesions of the brain. Thus, evoked potential studies sometimes reveal abnormalities missed by magnetic resonance imaging and vice versa. In patients with known CNS pathology, evoked potentials studies help to detect and localize lesions and also detect structural abnormalities in a variety of disorders [42].

VISUAL EVOKED POTENTIALS:

Visual evoked potentials are electrical potentials differences recorded from the vertex in response to visual stimuli .The VEPs represent the mass response of the cortical and possibly sub cortical areas. Normal cortical responses are obtained only if the entire visual system is intact and disturbances anywhere in the visual system can produce abnormal VEPs, therefore the localizing value of VEP is limited [33].

VEP is a gross electrical response recorded from visual cortex in response to a changing visual stimulus such as multiple flashes (flash visual evoked potential) or check board pattern (pattern onset / reversal VEP). It can detect functional loss in the visual pathway from retina to the visual cortex. The visual stimulus may be unstructured, as in a flashing light, or structured, as in some form of pattern to the flash stimulus or the stimulus may be patterned, as in checkerboard presented on a video display unit. The essential feature is that while the pattern changes, the overall illumination remain the same. Black squares go white and white become black

alternatively, the rate of the lightening of the dark squares being the same as that of the darkening of the light squares [43].

FLASH VER:

This is a most crude test and it indicates that light has been perceived. It is a fovea dominated response and is relatively unaffected by opacities in the cornea and the lens. It is therefore a useful test to grossly assess the intactness of the macula or the optic nerve.

PATTERN REVERSAL VER:

This depends on form sense and may give a rough estimate of visual acuity. It is more of fovea specific response. The timing of responses is more reliable than the amplitude [44]. The preferred stimulus for visual evoked potential testing is a checkerboard pattern of black and white squares.

NORMAL VEP FINDINGS:

The VEPs consist of a series of wave forms of opposite polarity. The negative waves are denoted by N and positive waves by P, which is followed by the approximate latency in ms. The commonly seen wave forms are N75, P100, and N145. The peak latency and peak to peak amplitudes of these waves are measured [45].

BASIS OF VEP ABNORMALITIES:

The VEP abnormalities may be latency prolongation, amplitude reduction and combined latency and amplitude abnormalities. The commonest cause of prolonged

P100 latency is demyelination in the optic pathways where the amplitude of P100 remains normal.

CLINICAL USES OF VEP:

The VEP study is a sensitive method for detecting the abnormalities in visual pathways especially anterior to the optic chiasma. It should be regarded as complementary to clinical examination and neuro-opthalmological investigations [33].

BRAIN STEM AUDITORY EVOKED POTENTIAL:

Brainstem auditory evoked potentials (BAEPs) are the potentials recorded from the ear and the scalp in response to a brief auditory stimulation to assess the conduction through the auditory pathway up to midbrain. The evoked potentials that appear following transduction of the acoustic stimulus by the ear cells create an electrical signal that is carried through the auditory pathway to the brain stem and from there to the cerebral cortex [45]. BAEPs comprise five or more waves within 10ms of the stimulus [33]. It may describe in terms of duration of onset of response [46].

BAEPs are useful to study in means of objectively and noninvasively the function of the auditory system, specifically the cochlea-auditory nerve-brainstem pathway, resulted in an extensive development of scalp recording of both near and far field potentials [39].

Early Auditory Evoked Potentials:

Early auditory evoked potentials (early AEPs) have also been reported to as short – latency auditory evoked potentials and corresponding to the responses recorded within the first 12msec after an auditory stimulus.

Middle-Latency Auditory Evoked Potentials:

Middle –latency auditory evoked potentials (MLPs) are potentials occurring between 12 and 50msec after acoustic stimulation. They can be recorded from transient or from high frequency stimuli.

Middle latency auditory evoked potentials has been clinically applied in the assessment of hearing threshold in infants and children, the identification of dysfunction in central auditory pathways, and the evaluation of the central auditory pathways in candidates for cochlear implants.

Late Auditory Evoked Potentials:

Evoked potentials occurring 50msec or more after acoustic stimulation are called slow or late auditory EPs. These potentials can be subdivided into exogenous components N1, P1 and P2, which are primarily dependent on characteristics of the external stimulus, and endogenous components such as P300, N400, CNV, and the mismatch negativity, which are more dependent on internal cognitive processes [39].

Normal BAEP Findings:

The BAEP consists of five or more distinct wave forms recorded within 10 ms of auditory stimulus and are generated in different regions of the peripheral and central

auditory pathways. Wave I originates from the peripheral portion of auditory adjacent to cochlea. Wave II originates from cochlear nucleus, Wave III from superior olivary nucleus, wave IV from lateral meniscus, and wave V from inferior colliculi [33]. The absolute latency, inter peak latencies and amplitude of wave forms of BAEPs were measured.

Interpretation of BAEPs:

BAEP interpretation requires identification and measurement of waves I, III, and V and the measurement of I-V and I-III inter peak intervals. These values should then be compared with the normal values for the patient's age and sex. First, absence of wave I with normal wave V probably reflects technical problems in recording. Second, absence of wave III is significant only when wave V is also missing or delayed. Third, BAEPs cannot be interpreted without considering the patients hearing status; conductive hearing loss and cochlear pathology may profoundly affect BAEP wave late latency and amplitude.

Utilization of Latency-Intensity functions permits differentiation of four types of pathologies:

1. Latency-intensity functions indicating conductive hearing loss. The functions are characterised by prolonged wave I and wave V with latency- intensity curves parallel to the normal curve. The I-V and I-III intervals are normal.
2. Latency-intensity functions indicating cochlear hearing loss. This type of abnormality accompanies high-frequency hearing loss of cochlear origin. It is characterised by a recruiting curve for wave I; that is, normal or mildly

prolonged wave I latencies with loud clicks and greater delays with decreased intensity, resulting in a steep curve. Wave V is not drastically affected, and its curve is less steep, resulting in a shortened I-V interval.

3. Latency-intensity functions indicating retrocochlear deficit type I. Wave I is prolonged with a steep latency-intensity function; Wave V is prolonged; therefore the I-V interval is prolonged. This type of abnormality has been reported in lesions affecting the eight nerves.
4. Latency-intensity functions indicating retro cochlear deficit type II. The wave I latency-intensity curve is normal. Wave V and the I-V inter peak interval are prolonged. The latency-intensity function of wave V and the I-V interval is variable. A delayed wave V with normal wave I latency signifies that the delay has occurred somewhere after wave I (that is, central to the auditory nerve).A variation of this type of abnormal BAEP is characterised by normal wave I and absence of succeeding wave [39].

BAEP findings may be abnormal at a time when imaging studies show no definitive abnormality [42].

CLINICAL APPLICATION:

1. BAEPs are effective in evaluating the integrity of the peripheral and central auditory pathways [39].
2. BAEPs have been used to detect subclinical brain stem pathology [42].
3. To assess the hearing in uncooperative patients and very young children.
4. To detect the degree of hearing loss in infants [45].

SOMATOSENSORY EVOKED POTENTIAL:

Somatosensory evoked potentials are the potentials generated by large diameter fibres (sensory fibres) in response to a sensory stimulus applied to them anywhere in their course, either in the peripheral or in the central portion of the pathway [45]. It depends on functional integrity of the fast-conducting large diameter group IA muscle afferent fibres and group II cutaneous afferent fibres and on the posterior column of the cord, although some fibres may follow a different, extralemniscal pathway [42].

The potentials recorded have different latencies and are accordingly called short, intermediate and long latency potentials.

Somatosensory evoked potentials are generally elicited by electrical stimulation of median and posterior tibial nerves.

Normal SEP Findings:

SEP components are defined by latency and polarity.

Components of median nerve SSEP:

The components of median nerve SSEP recording that are important to clinical interpretation include:

Erb's point potential - recorded as the afferent volley transverses the brachial plexus.

N13 - representing post synaptic activity in the central gray matter of the cervical cord.

P14- arising in the lower brainstem, most likely in the caudal medial lemniscus.

N18- representing post synaptic potentials generated in the rostral brain stem.

N20- representing activation of the primary cortical Somatosensory receiving area.

Normal Median SEP:

Erb as potential is described as N9, which is seen as a principle negative peak in the EP1-EPc channel. Spinal potential (N11) is a negative peak, which is recorded at spinous process of fifth cervical vertebra referred to EPc. The subsequent negative wave is higher in amplitude and is designated as N13.Children between 1 and 4 years normally have a prominent N11. The P14 potential is a positive peak widely distributed over the scalp and best recorded from Cc-EPc (Scalp – non cephalic Channel). In some normal individual, it may be of low amplitude and inconspicuous in all recording channels. It usually occurs 1ms after N13. The N18 is a negative peak broadly distributed over the scalp, beginning before N20, and usually apparent in non cephalic recording .i.e., Cc-EPc channel. The N20 is seen as a negative wave form in Cc-Fz and Cc-EP channels, and is usually identified as portion of negative potentials, just preceding the sharp drop off towards the succeeding cortical positive peak P25. In succeeding 40ms a series of cortical potentials are recorded which include N35, P45 and N60.

The following parameters are measured for the analysis of median SEP:

1. Latency
2. Amplitude
3. Inter peak Latency.

The N9 latency is measured in EP1-EPc channel from stimulus artefact to its peak and amplitude from the peak to the succeeding positive deflection. The N13 latency measured at the C5Sp-EPc channel from the stimulus artefact to the peak. The amplitude is measured from peak of N13 to the next deflection. The latency of N20 is measured to the point of maximum negativity just preceding the steep drop of P25 trough in Cc-fz channel. There are two important inter peak latencies (IPL), which are of clinical significance.

1. Brachial plexus to Spinal cord (N9-N13).
2. Central Sensory Conduction Time (N13-N20) [33].

MEASUREMENT OF THE CENTRAL CONDUCTION TIME (CCT):

One of the advantages of SEP recording in clinical routine is to permit an evaluation of the transit time of the ascending volley in the central segments of the somatosensory pathways.

Upper limb SEPs:

Various montages and procedures have been proposed for measuring the CCT depending on weather the aim is merely to detect a conduction slowing and to follow up CCT values during the evolution of a disease in the same individual, or to locate accurately the site where conduction velocity is slowed down. In all types of

montages the conduction in the proximal segment of brachial plexus roots can be evaluated by measuring the interval between the peaks of the supraclavicular N9 (or far-field P9) and the spinalN13 potentials. Techniques that provide the investigator with an index of global CCT abnormality are considered to yield enough information in many clinical situations; among these, the measurement of the interpeak between the cervical N13 and the parietal N20 components is the most widely used.

The global CCT can be evaluated by measuring the intervals either between peaks of N13 and N20 potentials (peak CCT) or between the onset of N11 and N13 potentials (onset CCT) [47].

FINDINGS OF EVOKED POTENTIALS IN HYPOTHYROIDISM:

Ladenson et al conducted a study of visual evoked potentials in hypothyroid patients and found prolongation of P100 latency ($P<0.05$) following 12 to 24 weeks of long term oral L-thyroxine treatment. The mean P100 latency was significantly reduced ($P<0.001$) and it was concluded that reversible alteration of this readily measurable parameter in hypothyroid patients reflects an effect of thyroid hormones on central nervous system function [9].

Khedr et al evaluated peripheral and central nervous system alteration in hypothyroidism. They found significant prolongation of P100 latency and decrease in the VEP amplitude and significant prolongation of absolute latencies and interpeak of the different waveforms of BAEPs in hypothyroid patients. In addition

to that , cognitive functions were significantly impaired in hypothyroid patient as measured by Wechsler intelligence scale and P300 [7].

Mastalgia et al conducted VEP studied in hypothyroid patients before and after with thyroxine and found P100latency was initially at the upper limit of or above of the normal range in seven cases and reported P100 latency returned to normal in four cases after the treatment with thyroxine and suggested that there is a reversible abnormality of conduction in the visual pathway in hypothyroidism [48].

Avramides et al studied VEP in hypothyroid patients before and after the treatment with thyroxine and found prolongation of P100 latencies in 7 out of 15 hypothyroid patients before treatment with thyroxine and reported P100 latencies was returned to normal in 4 patients when euthyroidism was achieved [49].

Salvi et al studied VEP in patients with TAO (thyroid associated ophthalmopathy) and observed prolongation of P100 latency in hypothyroid patient and showed that patient with TAO reveals asymptomatic optic nerve dysfunction in the absence of deterioration of visual acuity [50].

Ozkardes et al has evaluated the effects of acute hypothyroidism on brainstem auditory evoked potentials. They found significant prolongation of wave I is BAEP and explained low body temperature, diminished myelin production and alteration in cerebral metabolism may be the possible cause for this prolongation of wave I in BAEP [51].

A.R.D.thornton and **S.J.Jarvis** showed a statistically significant reduction in the amplitudes of waves III and V and significant increase in the I-V interpeak latencies

in hypothyroid patients. The measured abnormalities in I-V interpeak latencies may be explained on the basis of patients low body temperature [10].

Karlos Thiago Pinherio Dos Santo et al has done audiological evaluation in patient with acquired hypothyroidism and observed prolongation of absolute latency of wave I and the transient evoked otoacoustic emission were not present in a higher number of patients with hypothyroidism (20%) [52].

Yi-Hung Chou and **Pen-Jung Wang** was studied Auditory Brainstem evoked potentials in early treated congenital hypothyroidism and found pattern I, which causes prolongation of absolute latency of wave I, III, and V in hypothyroid patients [53].

Ritter showed that hearing loss can be the most common otorhinolaryngological manifestation of congenital and acquired hypothyroidism and auditory symptoms may happen alone or in association with vertigo and tinnitus [54].

Abdullah Ozkardes has evaluated the central nervous system alterations in acute hypothyroidism by somatosensory evoked potentials before and after the treatment with L-thyroxine. They found significant prolongation of mean central conduction time in both median and tibial nerve stimulated SSEPs in hypothyroid patient and showed improvement in central conduction time abnormalities on treatment with thyroxine and suggested that low body temperature, diminished myelin production and alteration in cerebral metabolism during acute hypothyroidism maybe the possible cause for the prolongation of central conduction time [12].

Coot J. Bongers–Shokking et al has evaluated SSEP in neonates with primary congenital hypothyroidism and observed prolonged latencies and prolonged central conduction time after the stimulus of median nerve and suggested that lack of thyroid hormones result in reduced myelin, synapse and dendrite formation [11].

Ozata et al has evaluated central motor conduction in thyroid patients and found significant prolongation of central motor conduction time in 4 of 20 hypothyroid patients. Improvement of CMCT abnormalities was observed in 1 of 4 hypothyroid patients after they become euthyroid [55].

Lai et al conducted somatosensory evoked potentials and peripheral nerve conduction studies in patients with primary hypothyroidism before and after treatment with thyroxine and reported 11 patients had significant prolongation of latencies of N9, N13, and N20 and only three patients had prolonged central conduction time and they showed significant improvement in SSEP and Peripheral nerve conduction studies after thyroxine treatment [56].

TREATMENT OF HYPOTHYROIDISM:

Clinical manifestation of Hypothyroidism is treated with Levothyroxine sodium (thyroxine). A primary advantage of levothyroxine therapy is that the peripheral deiodination mechanisms can continue to produce the amount of T_3 required in tissues under the normal physiologic control [15].

MATERIALS
AND
METHODS

MATERIALS AND METHODS

This study was conducted in the Department of Physiology, Thanjavur Medical College & hospital, Thanjavur. Case control type of study was done. The study period extended between may 2011 to 2012. The patients were selected from medicine and surgery department.

Out of 40 subjects, 7 males and 33 females with Hypothyroidism of age group (17-64 years) were selected. Diagnosis of hypothyroidism was confirmed when the total thyroxine level was below 4µg/dl and the thyrotropin level was above 4.5mU/ml. A history was taken, and a complete medical examination and neurological examination were out for every patient. Out of 40 controls, 10 males, 30 females, of age group (17-64 years) were selected.

Inclusion criteria:

- Patients with biochemical evidence of hypothyroidism (Serum total thyroxine < 4µg/dl, TSH > 4.5mU/ml.

Exclusion criteria:

- Diabetes mellitus.
- Neurological disorders.
- Psychiatric illness.
- Seizures.
- Hypertension.

- Eye diseases (severe myopia, cataract, glaucoma etc).
- Collagen disease.
- Renal impairment.
- Drug abuse.

The nature of study was explained to all the subjects. Informed written consent was obtained from all the participants. The experimental protocol was approved by the ethical committee.

The thyroid profile was carried out using ELISA method. The following electrophysiological parameters are studied:

- VEP (Visual Evoked Potential)
- BAEP (Brain stem Auditory Evoked Potential)
- SSEP (Somatosensory Evoked Potential)

All these parameters are recorded using four channel digital polygraph. Digital intex colour monitor, 17''model no: IT-173 SB.

METHOD OF RECORDING VEP, BAEP, SSEP:

Electrodes are positioned using 10-20 electrode placement system [58].

VISUAL EVOKED POTENTIAL:

Pre test instructions:

1. The subject was told about the procedure of the test and got informed consent.

2. The subject is asked to avoid applying hair spray or oil after the last hair wash.
3. If the subject uses optical lenses, glasses should be worn during the test.
4. The subject is instructed not to use any miotics and mydriatics 12 hours before the test.
5. Full ophthalmological examination was carried out to determine visual acuity, pupillary diameter and field of vision.
6. The room should be quite and comfortable.

RECORDING OF VEP:

Instrument setting for VEP:

Setting	**VEP**
Sweep	20msec
Sensitivity	10µv
Low cut	2Hz
High cut	200Hz
Pulse	1/sec
Pulse width	0.1msec
notch	Off
Recordings	100 average was recorded using Checker board pattern stimulus given

PROCEDURE:

The pattern-shift visual evoked potential was measured separately for each eye by following steps.

1. The skin is prepared by abrading and degreasing.
2. The recording electrode is placed at O_Z using electrode paste as per 10-20 international system of EEG electrode placement.
3. The reference is placed at FPz.
4. The ground is placed at the vertex (i.e.) at Cz
5. The procedure is conducted in dark room with subject sitting at a distance of a 1 meter from the VEP screen showing pattern reversal stimuli in check board pattern with reversal rate 2/sec, contrast 50-80%, check size 28-32 of arc and number of trails is 100.
6. From the waveform obtained (Figure 2) P100 latency is marked. P 100 is a positive potential at about 100ms.

VEP SHOWING P100 LATENCY

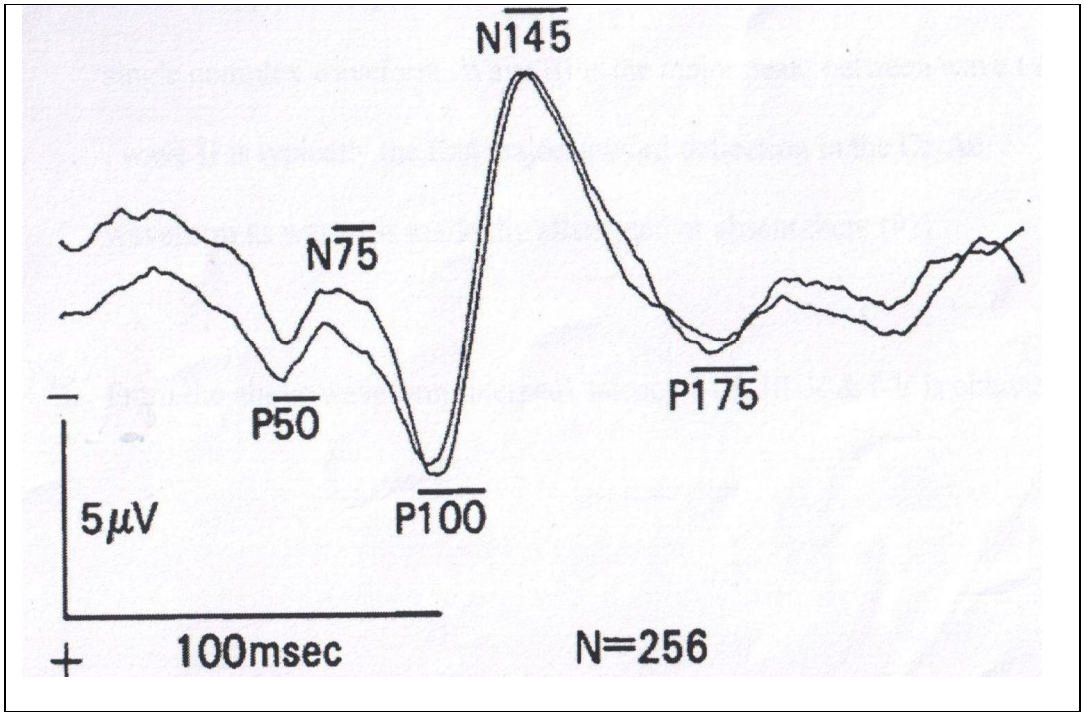


FIGURE 2

BRAINSTEM AUDITORY EVOKED POTENTIAL:

Pre test instruction:

1. The subject was told about the procedure of the test and got informed consent.
2. The subject is asked to avoid applying hair spray or oil after the last hair wash.

3. Examination of external ear, Rinne's test, and Weber's test are carried out.
4. Subject is made to fully relax.
5. Mild hypnotics can be used to ensure relaxation.
6. Room should be quite and comfortable.

RECORING OF BAEP:

Instrument setting for BAEP:

Settings	**BAEP**
Sweep	5msec
Sensitivity	10µv
Low cut	100Hz
High cut	10Hz
pulse	11/sec
Pulse width	0.1 msec
notch	On
Decibels	60Db
Recordings	100 average was recorded using Click sound as stimulus.

Procedure:

1. The skin is prepared by abrading and degreasing.
2. The electrode placement is at

   Channel 1 =Cz-Ai (ipsilateral ear)

   Channel 2= Cz-Ac (contra lateral ear).

   Ground electrode is placed at 20%from the nasion Fz.

3. Head phones are placed on the ears for delivery of the auditory stimulus.

   Clicks are delivered at the rate of 8-10/sec. Intensity to set at 60 db.

   About 100 average is taken.
4. From the waveform (figure 3) obtained wave I and V is marked first.

   Wave I is the first major up going peak usually follow a small stimulus artefact.
5. Wave V appears at approx 6ms and is often combined with wave IV in to a single complex waveform. Wave III is the major peak between wave I and V .Wave II is typically the first major upward deflection in the Cz –Az waveform as wave I is markedly attenuated or absent there.
6. From the above waveform inter peak latency I-III, III-V and I-V is obtained.

BAEP SHOWING WAVEFORMS I TO V

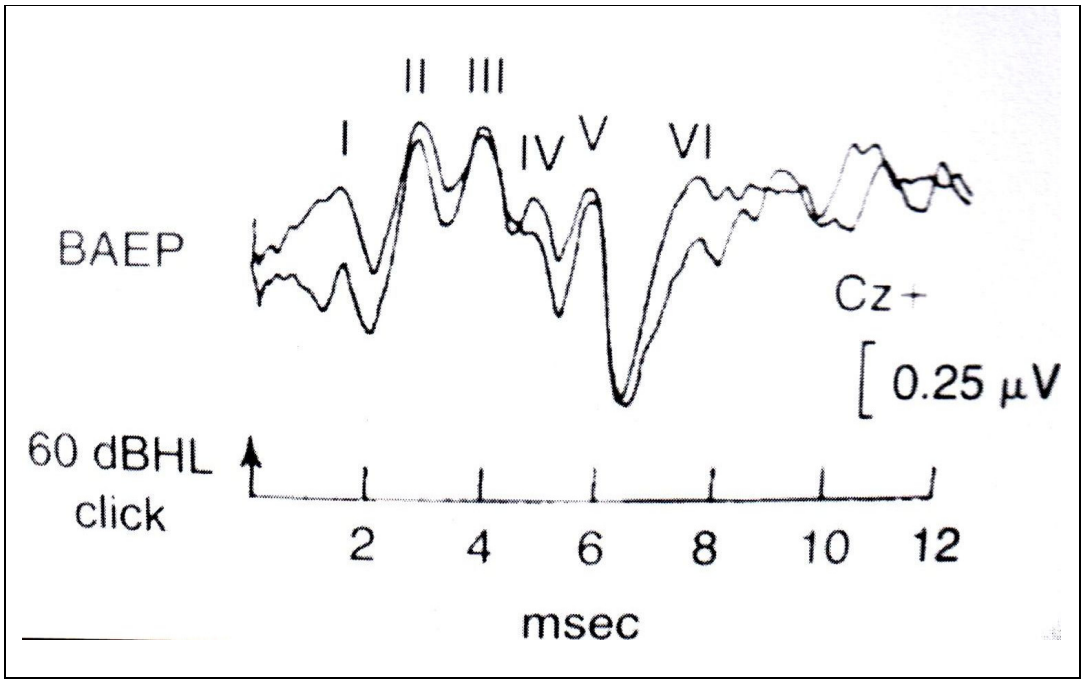


FIGURE 3

SOMATOSENSORY EVOKED POTENTIAL OF MEDIAN NERVE:

Pre test instruction:

1. The subject was told about the procedure of the test and got informed consent.
2. The subject is asked to avoid applying hair spray or oil after the last hair wash.

3. History obtained to rule out nerve injury and Median nerve examination carried out.
4. The subject is made to fully relax in supine position with head supported (in order to relax neck muscles).
5. Mild hypnotic can be used to ensure relaxation.
6. The room should be quite and comfortable.

RECORDING OF SSEP:

Instrument setting for SSEP:

Settings	**SSEP**
Sweep	5msec
Sensitivity	10µv
Low cut	30 Hz
High cut	3KHz
Pulse	2/sec
Pulse width	0.1msec
Notch	Off
Recordings	100 average was recorded using 5mAmp Current.

Procedure:

1. The skin is prepared by abrading and degreasing.
2. The electrodes are placed as

Channel 1	Cc-Fz
Channel 2	Cc-EPc
Channel 3	C5Sp-EPc
Channel 4	EPi-EPc

3. The recordings obtained from the subject in lying posture with neck relaxed, by stimulating the median nerve at the wrist.
4. Number of trials 100, analysis time 40ms, keeping low filter at 1-3 HZ [33].
5. From the waveform (figure 4), the following are measured N9 latency is measured in EPi-EPc channel from stimulus artefact to its peak.

   N13 latency is measured in Ci-EPc or Cc-Fz channel.

   N9 -Distal brachial plexus.

   N13 -rostral cervical spinal cord

   N20 -thalamo cortical radiations.

Brachial plexus to spinal cord = N19-N13

Central sensory conduction time = N13-N20

Cortical latency = N20

SSEP WAVEFORM

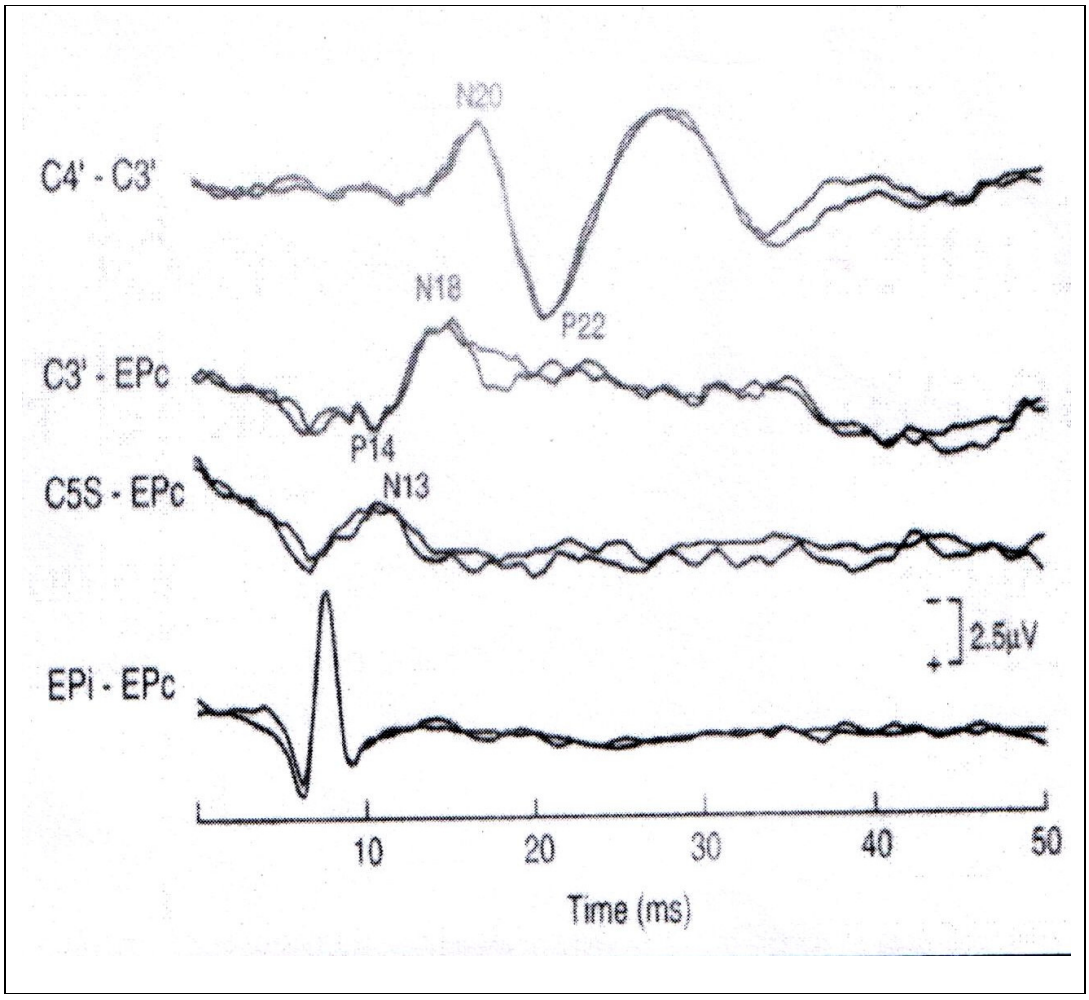


FIGURE 4

Statistical method:

Electrophysiological parameters were analysed by using statistical package SPSS version 18 and statistical analysis was done by student‘t’ test.

Fig: 2 VEP RECORDING

Fig 3: VEP WAVEFORM

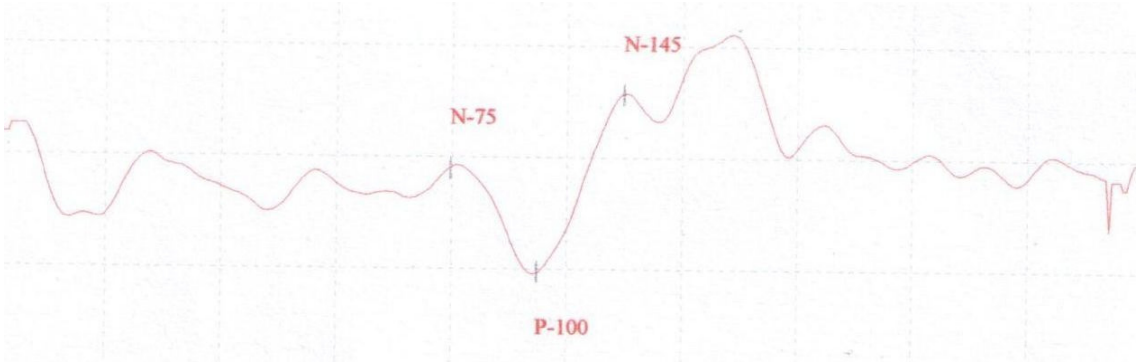


Fig 4: RECORDING OF BAEP

Fig 5: BAEP WAVEFORM

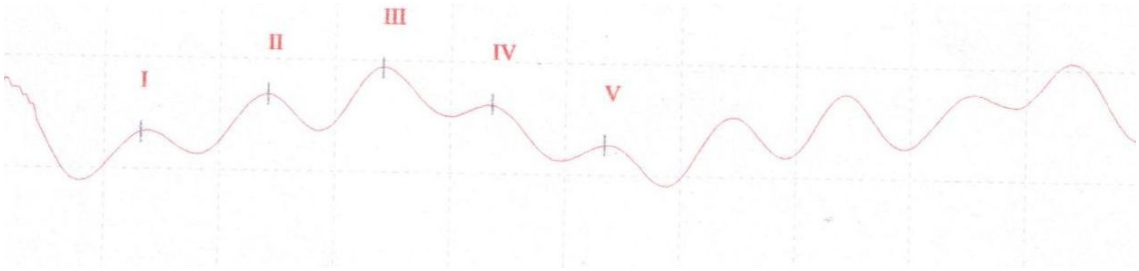
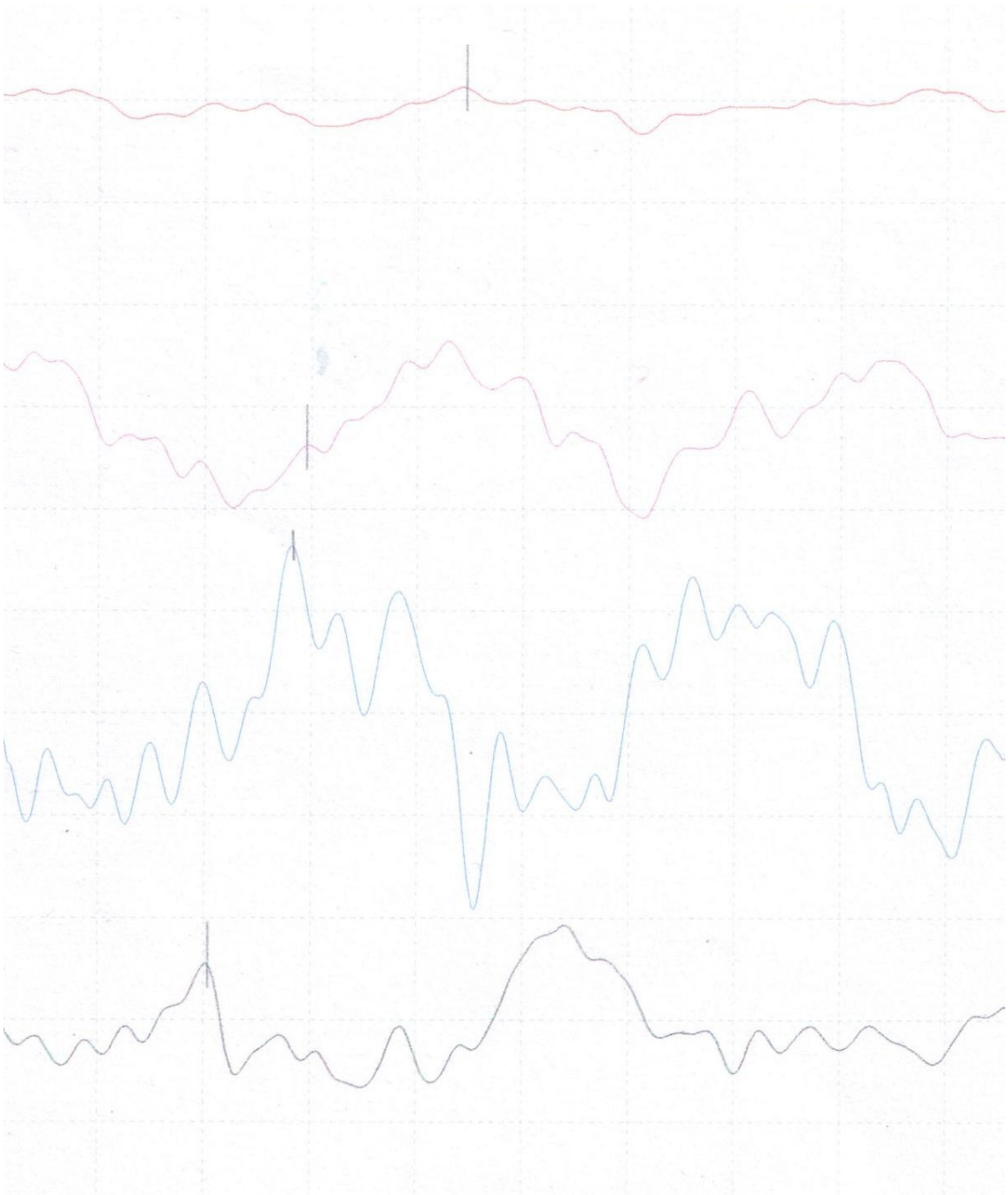


Fig 6: SSEP WAVEFORM



RESULTS

RESULTS

Out of 80 subjects, 40 were hypothyroid patients forming the study group and remaining 40 were normal subjects forming control group.

In this study hypothyroid patients who form the study group were in age group 17-64 years, mean 39.64 and the subjects in control groups were in the age group 17-64 years, mean 35.75.

The mean values and their standard deviation for the control group and the study group of hypothyroids were tabulated.

The two groups differ significantly in various electrophysiological parameters like VEP, BAEP, and SSEP. 'P'value was derived from data analysis by using statistical package SPSS version 18 and statistical analysis was done by student't' test. The statistical significance was considered at p value < 0.05.

DESCRIPTIVE STATISTICS

Table -1: serum levels of T_3, T_4, and TSH in hypothyroid patients

Item	Hypothyroid (n=40)			
	Min.	Max.	Mean	S.D
T3 (ng/dl)	0.04	1.60	0.3867	0.37450
T4 (µg/dl)	0.68	3.97	2.3900	0.74477
TSH (mIU/L)	5.02	32.00	9.5910	5.30216

Table -2: serum levels of T_3, T_4, and TSH in control group

Item	Control (n=40)			
	Min.	Max.	Mean	S.D
T3 (ng/dl)	0.34	5.60	1.1458	0.88295
T4 (µg/dl)	5.32	24.00	9.0480	3.98983
TSH (mIU/L)	0.50	4.30	2.0575	0.95195

Table-3: Electrophysiological findings in hypothyroid patients (n=40)

Parameters	Min	Max	Mean	Std. Deviation
VEP				
P100 Latency (ms)	91.50	114.50	103.66	5.65
BAEP				
I-III Latency (ms)	1.575	3.625	2.58325	0.548135
III-V Latency (ms)	1.30	3.20	2.32475	0.49836
I-V Latency (ms)	3.875	6.57	4.89475	0.64379
SSEP (Median Nerve)				
N20 (ms)	20.25	28.935	24.3379	2.09836
N13 (ms)	12.69	18.935	15.18555	1.469805
N9 (ms)	7.75	11.75	9.8344	1.01036
CCT(N20-N13) (ms)	3.55	13.65	8.72625	2.175545

Table-4: Electrophysiological findings in control group (n=40)

Parameters	Min	Max	Mean	Std. Deviation
VEP P100 Latency(ms)	84.75	101.50	95.69	4.10
BAEP I-III Latency(ms)	1.275	3.14	2.172	0.47811
III-V Latency(ms)	1.16	2.81	1.88	0.40041
I-V Latency(ms)	3.115	5.2	4.02525	0.461345
SSEP (Median Nerve) N20(ms)	19.00	23.00	20.31885	0.94169
N13(ms)	11.87	15.94	13.23	0.71382
N9(ms)	6.38	10.44	8.973	0.8824
CCT(N20-N13) (ms)	5.45	9.7	7.08125	1.02103

PARAMETERS	HYPOTHYROID n =40	CONTROLS n= 40	P value
	(Mean ± SD)	(Mean ± SD)	
TRIIODOTHYRONINE [T3] (ng/dl)	0.3867±0.37450	1.1458±0.88295	0.001
THYROXINE [T4] (µg/dl)	2.3900 ± 0.74477	9.0480±3.98983	0.001
THYROTROPIN [TSH](mUI/L)	9.5910 ±5.30216	2.0575±0.95195	0.001

Table -5

The table -5 shows that there is a significant difference between control group and hypothyroid group in T_3, T_4, TSH levels. The statistical test used in the above table was student‘t’ test.

PARAMETERS	HYPOTHYROID n =40	CONTROLS n= 40	P value
	(Mean ± SD)	(Mean ± SD)	
VEP			
P100 latency (ms)	103.66 ± 5.65	95.69 ± 4.10	0.001
BAEP			
I –III Latency (ms)	2.58325 ± 0.54813	2.172 ± 0.4781	0.003
III –VLatency(ms)	2.32475± 0.49836	1.88 ± 0.4004	0.001
I – V Latency (ms)	4.89475 ±0.64379	4.02525 ± 0.4613	0.001
SSEP(Median Nerve)			
N20 (ms)	24.34 ±2.0983	20.3188 ± 0.9416	0.001
N13 (ms)	15.1855 ± 1.4698	13.23 ± 0.71382	0.001
N9 (ms)	9.8344 ± 1.0103	8.973± 0.8824	0.001
CCT			
(N20 - N13) (ms)	8.72625 ± 2.17554	7.08125 ±1.02103	0.001

Table -6

The table -6 shows that there is a significant difference between control and hypothyroid group in latency P100 VEP, latency and interpeak latencies of BAEP, latency N20, N13, N9 and Central conduction time. The statistical test is used in the above table was student‘t’ test.

Triiodothyronine level in hypothyroid patients show mean value 0.3867±0.37450 and in control group it is 1.1458±0.88295 with P value 0.001 showing the difference Significant.

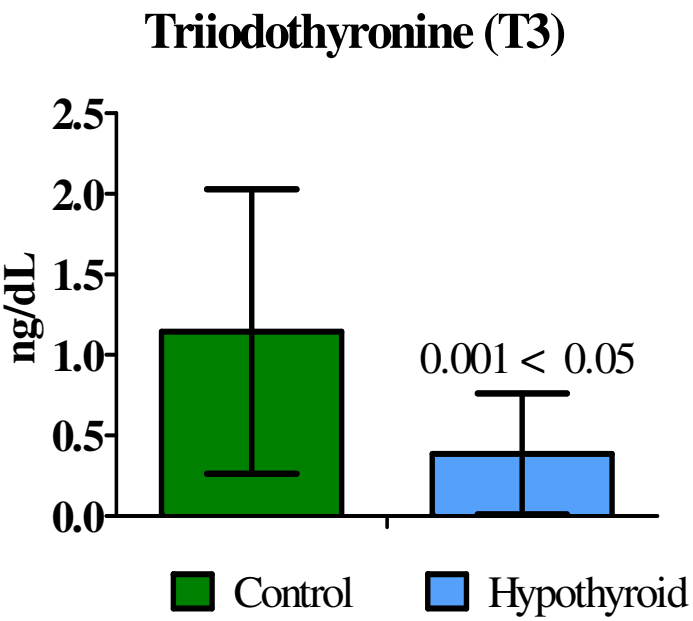


Figure 7: Show significant difference in Triiodothyronine level between control group and hypothyroid patients.

Thyroxine level in hypothyroid patients show mean value 2.39±0.74477 and in Control group it is 9.048±3.98983 with P value 0.001 showing the difference is Significant.

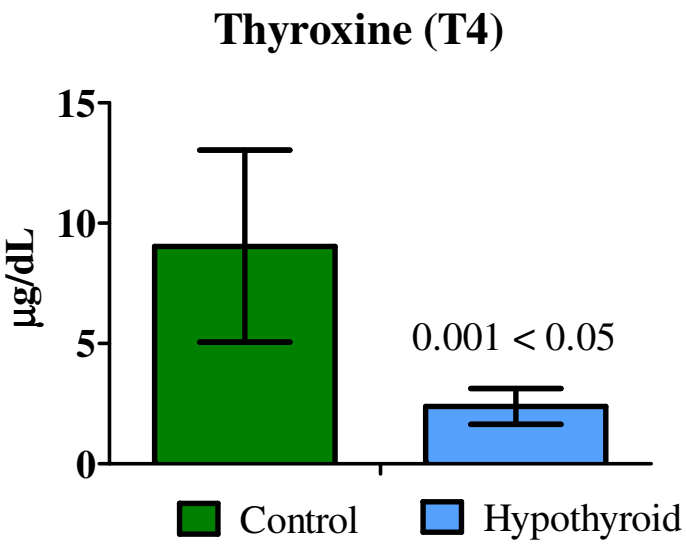


Figure 8: Show significant difference in Thyroxine level between control group and hypothyroid patients.

Thyrotropin (TSH) levels in hypothyroid patients show mean value 9.5910±5.30216 and in control group it is 2.0575 ±0.95195 with P value 0.001 showing the differences Significant.

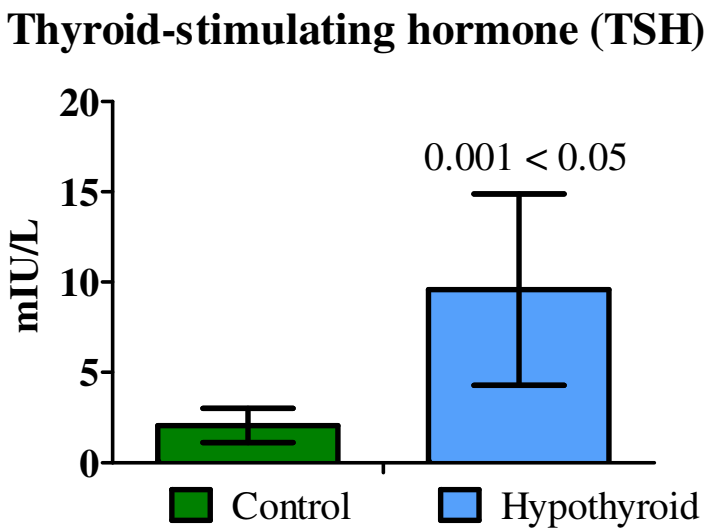


Figure 9: Show significant difference in TSH level between control group and hypothyroid patients.

VEP P100 latency in hypothyroid patients show mean value 103.66±5.65 and in Control group it is 95.69±4.10 with P value 0.001 showing the difference is Significant.

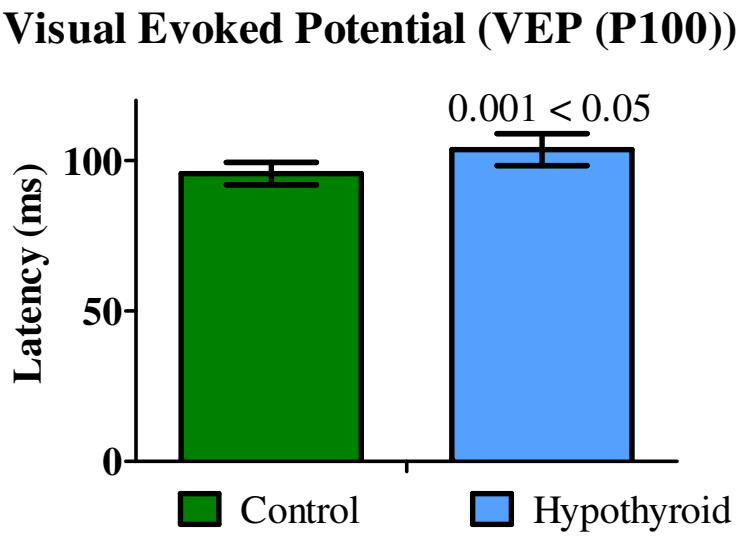


Figure 10: Comparison of VEP P100 latency between control group and hypothyroid patients.

BAEP I-III latency in hypothyroid patients showing value 2.58325±0.548135 and in the control group it is 2.172 ±0.47811 with P value 0.003 showing the difference is significant.

BAEP III-V latency in hypothyroid patients show value 2.32475±0.49836 and in the control group it is 1.88±0.40041 with the P value 0.001 showing the difference is significant.

BAEP I-V latency in hypothyroid patients show value 4.89475±0.64379 and in the control group it is 4.02525±0.461345 with the P value 0.001 showing the difference is significant.

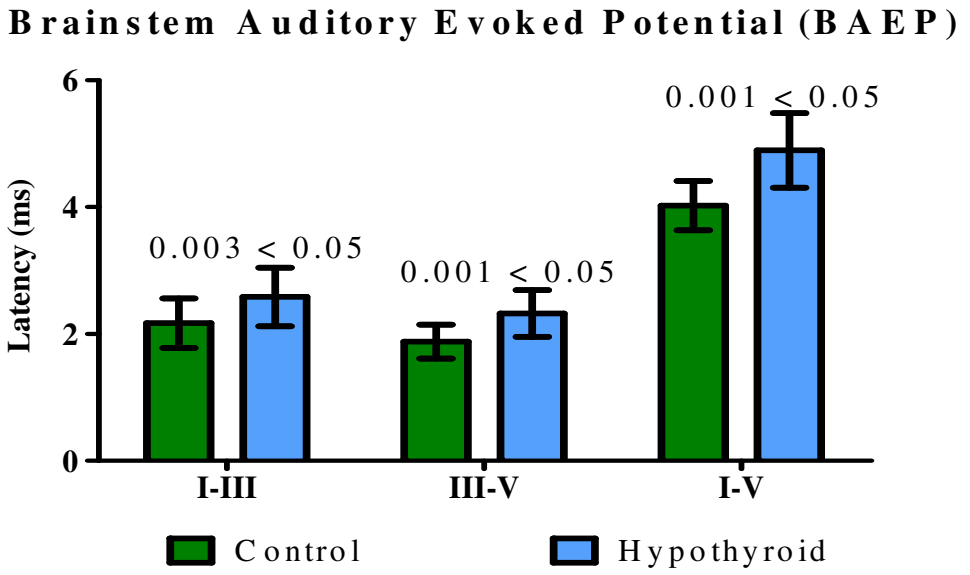


Figure 11: Comparison of BAEP I-III, III-V, I-V interpeak latency between control group and hypothyroid patients.

SSEP (median) N20 latency in hypothyroid patients show value 24.3379±2.09836 and in the control group it is20.31885±0.94169 with the P value 0.001 showing the difference is significant.

SSEP (median) N13 latency in hypothyroid patients show value15.18555±1.469805 and in the control group it is 13.23±0.71382 with the P value 0.001 showing the difference is significant.

SSEP (median) N9 latency in hypothyroid patients show value9.8344±1.01036 and in the control group it is 8.973±0.8824 with the P value 0.001 showing the difference is significant.

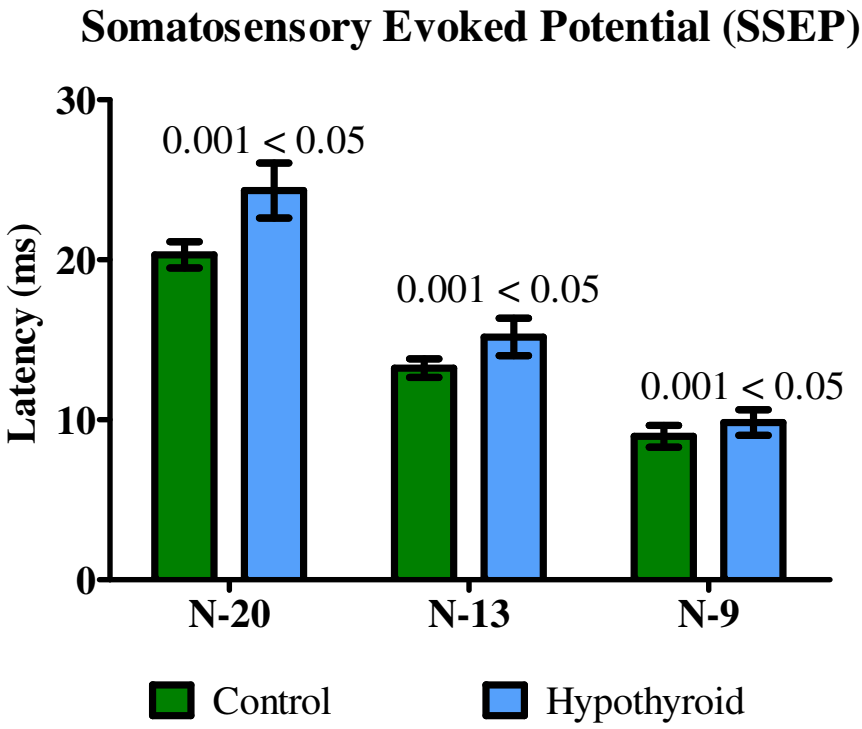


Figure 12: Comparison of Latency of N-20, N-13, and N-9 between control group and hypothyroid patients.

SSEP (median) Central Conduction Time (N20-N13) latency in hypothyroid patients Show value 8.72625±2.175545 and in the control group it is 7.08125±1.02103 with the P value 0.001 showing the difference is significant.

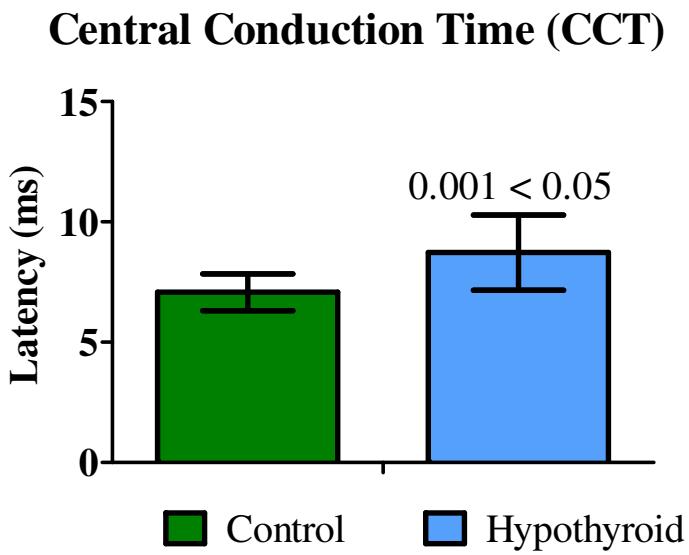


Figure 13: Comparison of central conduction time between control group and hypothyroid patients.

DISCUSSION

DISCUSSION

In this study, the electrophysiological parameters are evaluated in patients with hypothyroidism. The results of the electrophysiological study were compared between 40 patients with hypothyroidism and 40 healthy euthyroid subjects.

Hypothyroidism, particularly when subclinical, is the most common endocrinological disorders, with a prevalence ranging from 4 to 10% of the adult population. Hypothyroid states have a multiple effects on structure, perfusion, and function of the CNS [38].

Central nervous system dysfunction is an important consequence of thyroid hormone deficiency. Although the peripheral nervous system has been extensively studied in hypothyroid patients by a variety of techniques, quantitation of the central nervous system derangements has been less precise (Ladenson). However clinical observations and a wide range of neuro imaging, electrophysiological and neuropathologic investigations conducted in recent decades have confirmed a deleterious effect of hypothyroidism on the morphological and functions of the CNS. In a recent study, PET and SPECT measurement of cerebral blood flow in hypothyroidism was associated with global, diffuse hypoperfusion.

However, early involvement of the CNS, unlike the symptoms of peripheral neuropathy is usually subclinical and can be detected only through

neurophysiological investigations. Measurements of stimulus conduction within the CNS by means of evoked potentials allow sensitive and reliable detection of subclinical changes.

In this study, P100 latency of VEP is prolonged in patients with hypothyroidism and was found to be statistically significant.

This study results are consistent with those of Khedr et al, Mastalgia et al, Ladenson et al, Salvi et al, Avramides et al, Ladenson et al showed significant prolongation of P100 latency of VEP in hypothyroid patients, and reported that P100 latency of VEP was returned to normal on treatment with L- thyroxin and suggested that thyroid hormones have been shown to affect myelin synthesis, which is an important factor in determining the speed of impulse transmission along complex polysynaptic pathways such as those mediating the visual evoked potential. The reversible alteration of this readily measurable parameter in the hypothyroid patients reflects an effect of thyroid hormones on Central Nervous System.

In this study, prolongation in the latency of Brain Stem Auditory Evoked Potentials (BAEP) I-III, III-V and I-V was found in patients with hypothyroidism and was statistically significant.

Hearing is one of the most sensitive functions controlled by thyroid hormone, and early onset hypothyroidism (or) iodine deficiencies is known causes of deafness in humans and rodent model species. The thyroid hormone is required for the timely

co- ordination of the complex set of differentiation events in maturing cochlea. Several studies ([10, 51- 54]) show prolongation of latency and inter peak latency of BAEPs.

Metin Ozata et al showed that low body temperature, diminished myelin production and alteration in cerebral metabolism during acute hypothyroidism may be the possible explanations for the prolongation of wave I latency of BAEP.

Ritter in his study showed that the symptoms relating to auditory pathway in hypothyroidism may be due to hyper osteosis of the otic capsule or central nervous system damage.

In this study, the latency of median SSEP N20, N13, N9 and central conduction time are prolonged in hypothyroid patients indicating delayed peripheral and central nerve conduction and was statistically significant.

The results of the present study agreed with those of Abdullah Ozkardes et al, Coot J Bongers – Shocking et al. Adullah Ozkardes et al showed prolongation of latency of N20, N13, N9 and prolongation of central conduction time acute hypothyroidism and suggested that low body temperature, diminished myelin production and alteration in cerebral metabolism during acute hypothyroidism may be the possible explanations for the prolongation of central conduction time.

The latency depends on an intact, myelinated nerve as myelin and saltatory conduction are essential for fast action potential propagation in normal subjects. Slowing of conduction velocity or propagation of latency usually implies defect in myelination. The prolongation of cortical wave latency P100, BAEP I-III, III-V, I-V

interpeak latency, SSEP N20, N13, N9 latency and prolongation of central conduction time are more significant that, it suggests there is central nervous system involvement.

The present study results signify that there is a definite neurological deficit in thyroid deficiency, which can involve the central nervous system at much earlier stage.

In hypothyroidism mentation is slow and cerebrospinal fluid protein is elevated. They affect mitochondrial oxidative activity, synthesis, degradation of proteins and sensitivity of tissue to catecholamines and hence demyelination occurs due to oxidative damage to myelin membrane and oligodendroglial cells. Thus the present study results from VEP, BAEP, and SSEP data indicated hypothyroidism affect myelination.

Peripheral and central nervous system alterations in hypothyroidism have shown that CNS is more vulnerable to the effects of hypothyroidism than peripheral nervous system. Therefore electrophysiological studies were suggested to be performed in hypothyroid subjects early in course of thyroid deficiency in order to detect nervous system involvement.

CONCLUSION

CONCLUSION

The result of present study shows that there is involvement of Central Nervous System in hypothyroidism. The hypothyroid patients show prolongation of latency in electrophysiological studies.

Electrophysiological parameters like P100 latency of VEP, latency and inter peak latencies of I-III, III-V, I-V of BAEP and peripheral and cortical latencies of SSEP of median nerve were evaluated. The observation shows prolongation of latencies suggestive of central nervous system involvement in hypothyroidism.

This study suggests that periodic evaluation of hypothyroid patients to electrophysiological test will help in monitoring the progress of neuropathy and earlier detection of nervous system involvement to reduce the morbidity of hypothyroid patients.

However further studies are required to evaluate the correlation between the electrophysiological parameters and thyrotropin (TSH) level and duration of disease so that preventive measures can be suggested to prevent the central nervous system involvement.

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ANNEXURE

CONSENT FORM

Dr. M.Jayanthi, post graduate student in the Department of physiology, Thanjavur Medical College, Thanjavur is doing a comparative study on electrophysiological parameters in hypothyroidism. The procedures have been explained to me clearly. I understand that there are no risks involved in the above procedure. I hereby give my consent to participate in this study. The data obtained here may be used for research and publication.

Signature:

Name:

Place:

PROFORMA

EARLY DETECTION OF CNS INVOLVEMENT IN HYPOTHYROIDISM BY ELECTROPHYSIOLOGICAL STUDY

PATIENT NAME:

AGE: **SEX:**

OCCUPATION: **ADDRESS:**

PRESENT HISTORY:

PAST HISTORY:

[Known Diabetic/ hypertension/Seizure/Psychiatric/ neurological disorders /visual/ auditory deficit]

PERSONAL HISTORY:

TREATMENT HISTORY:

GENERAL EXAMINATION:

Ht: Wt:

Higher function / Anemia / Cyanosis / Clubbing / Icteric / Pedal edema / Lymphadenopathy**.**

VITAL SIGNS:

PR: RR: BP: TEMP:

SYSEMIC EXAMINATION:

Respiratory System:

Cardiovascular System:

Abdominal Examination:

Central Nervous System Examination:

- Examination of eye:
- Examination of ear:

GENERAL INVESTIGATION:

URINE: Albumin /sugar

Blood glucose:

SPECIAL INVESTIGATION:

T_3: T_4: TSH:

PROFORMA

EARLY DETECTION OF CNS INVOLVEMENT IN HYPOTHYROIDISM BY ELECTROPHYSIOLOGICAL STUDY

VEP

PARAMETERS		P 100(ms)	R-L(ms)	AMPLITUDE(μv)	DURATION
OBTAINED VALUE	RIGHT				
	LEFT				
INFERENCE					

BAER

WAVE LATENCY(ms)		I	II	III	IV	V	VI	I-III IPL	III-V IPL	I-V IPL
OBTAINED VALUE	RIGHT									
	LEFT									
INFERENCE										

SSEP

PARAMETERS		MEDIAN NERVE						
		LATENCY (ms)				AMPLITUDE(μV)		
		N9	N20-N9	N20-P13	P13-N9	N9	P13	N20
OBTAINED VALUE	RIGHT							
	LEFT							
INFERENCE								

ABBREVIATIONS USED IN THIS STUDY

BAEP **:** Brain stem auditory evoked potential.

CCT : Central conduction time.

CMAP : Compound muscle action potential.

CNS : Central nervous system.

DIT : Diiodotyrosine.

EEE : Electroencephalography.

EPs : Evoked potentials.

FNAC : Fine needle aspiration cytology.

IPL : Interpeak latency.

MIT : Monoiodotyrosine.

MLPs : Middle latency auditory evoked potentials.

PET : positron emission tomography.

RAIU : Radioactive iodine uptake.

SPECT : Single photon emission computer tomography.

SSEP : Somatosensory evoked potential.

TRH : Thyrotropin releasing hormone.

TSH : Thyroid stimulating hormone / thyrotropin.

T_3 : Triiodothyronine.

T_4 : Thyroxine.

VEP : Visual evoked potential.

ELECTROPHYSIOLOGICAL PARAMETERS AND THYROID PROFILE - CONTROL GROUP

s.no	AGE/ SEX	T3 ng/dl	T4 µg/dl	TSH mIU/l	VEP P_{100} LATENCY ms		BAEP LT (ms)			BAEP RT (ms)			SSEP LT (ms)				SSEP RT (ms)			
					LT	RT	I-III	III-V	I-V	I-III	III-V	I-V	N-20	N-13	N9	CCT	N20	N13	N9	CCT
1	58/F	0.45	6	1.2	96	98.5	2.93	1.7	4.63	2.93	1.6	4.53	19.4	13.8	9.25	5.6	20.9	13.5	7.75	7.4
2	23/F	0.56	8	0.8	86.5	88.5	1.95	2.62	4.57	1.7	1.6	3.3	19.1	13.3	9.25	5.8	20.5	13.3	9.25	7.2
3	32/F	1.23	7.8	1.36	99.5	98.5	1.9	1.73	3.63	1.88	1.97	3.85	20.5	12.6	8	7.9	21.9	12.8	8.88	9.1
4	58/F	0.87	5.6	1.97	99.5	93.5	2.12	1.95	3.03	1.79	2.04	3.48	20.4	12.4	8.75	8	19.4	13.6	9.38	5.8
5	59/F	1.14	5.4	1.43	84.5	85	2.93	1.5	4.43	2.83	1.35	4.18	20	14.1	8.38	5.9	21.5	13.4	9.12	8.1
6	23/M	1.56	6.2	1.3	97.5	95	2.26	2.04	4.03	1.65	1.82	3.47	19.3	13.5	8.38	5.8	19.3	13.4	8.62	5.9
7	43/F	0.98	7.3	2.94	100	97.5	1.98	1.5	3.48	2.35	1.13	3.48	20.6	13.8	9.62	6.8	19.6	13.1	8.62	6.5
8	34/F	0.68	8.5	1.49	98	101	2.22	2.28	4.5	1.62	1.58	3.2	20.5	12.3	8.88	8.2	19.9	12.3	8.12	7.6
9	29/F	0.46	7.2	2.03	99	98.5	2.43	1.57	4	1.57	2.78	4.35	19.1	13	9.25	6.1	20.9	12.9	9.88	8
10	32/F	0.96	6.4	3.6	91.5	96.5	1.95	2.13	4.08	1.94	2.16	4.1	19.3	12.8	7.38	6.5	19.3	11.8	8.62	7.5
11	34/M	2.3	10.2	0.82	96	96	2.2	2.28	4.48	2.72	1.96	4.68	20	12.8	8.62	7.2	19.1	12.4	9.25	6.7
12	33/M	1.18	5.32	2.55	91	89	1.78	2.07	3.85	1.65	1.87	3.52	20.4	12.9	9.5	7.5	19.4	13.1	9	6.3
13	27/M	1.46	6.2	2.06	94	90	2.82	1.43	4.25	2.6	2.92	4.2	20.6	12.1	9.5	8.5	21.5	12.9	9.62	8.6
14	36/F	2.1	11	2.07	99	101	1.45	2.35	3.8	2.98	1.75	4.73	20	13.3	9.75	6.7	19.8	13.6	8.38	6.2
15	35/F	1.96	16	0.5	94.5	94.5	2.6	1.53	4.13	2.33	2.12	4.45	19.5	13.9	10.5	5.6	19.5	12.4	9	7.1
16	44/F	0.87	12	2	101	100	1.96	1.54	3.5	2.7	1.67	4.37	19	13	9	6	20.8	13.5	9.62	7.3
17	41/F	0.98	21	0.68	99	99.5	2.07	2.12	4.19	1.8	2.2	4	20.3	13.3	9	7	19.5	12.9	8.38	6.6
18	28/F	0.44	24	0.56	93.5	94.5	2.17	2.7	4.87	2.65	1.79	4.44	19.5	13.8	9.12	5.7	20.8	13.8	8.75	7
19	62/F	0.98	9.6	1.42	93.5	91.5	1.98	1.62	3.6	1.85	1.8	3.65	20	12.8	6.25	7.2	21.5	11.6	6.5	9.9
20	30/F	1.02	12.6	1.93	97	98	2.5	1.62	4.12	2.7	1.83	4.53	20.4	13.4	9	7	19.1	13	9.5	6.1

ELECTROPHYSIOLOGICAL PARAMETERS AND THYROID PROFILE - CONTROL GROUP

s.no	AGE/ SEX	T3 ng/dl	T4 µg/dl	TSH mIU/l	VEP P_{100} LATENCY ms		BAEP LT (ms)			BAEP RT (ms)			SSEP LT (ms)				SSEP RT (ms)			
					LT	RT	I-III	III-V	I-V	I-III	III-V	I-V	N-20	N-13	N9	CCT	N20	N13	N9	CCT
21	22/F	1.16	7.23	2.16	96	97.5	3.28	2.14	5.42	3	1.98	4.98	20.1	13.1	9.5	7	20.6	13.3	9.88	7.3
22	31/F	0.46	10.6	1.53	100	99.5	1.63	2.35	3.98	1.86	1.47	3.33	19.1	13	10	6.1	20.4	14.9	9	5.5
23	45/M	0.9	12.6	1.6	99.5	96	1.64	2.48	4.12	2.03	1.18	3.21	19.9	13.3	9.12	6.6	19.1	13.8	9.38	5.3
24	18/F	0.76	7.4	2.49	87	90.5	2.08	1.7	3.78	1.7	1.97	3.67	20.8	13.6	10.4	7.2	21.9	13.8	8.75	8.1
25	33/F	1.02	12.4	2.43	98.5	100	1.85	1.68	3.53	1.57	2.13	3.7	21.6	13.1	9.62	8.5	21	13.9	9.12	7.1
26	29/M	0.64	6.8	1.34	100	97.5	2.6	1.19	3.79	1.56	2.22	3.78	19.3	13.1	7.25	6.2	20.1	13.4	9.88	6.7
27	36/M	0.58	10.6	2.8	102	96.5	2.08	2.42	4.5	2.18	2.1	4.28	20.5	13	9.12	7.5	20.1	13.4	9.88	6.7
28	19/M	0.34	5.6	2.16	94	95.5	3.14	1.43	4	2.85	1.63	4.2	20	13.4	8.88	6.6	20	13	9	7
29	19/F	0.48	9.8	0.58	94	95.5	2.55	1.45	4	2.23	1.29	3.52	19.5	13.1	7.12	6.4	19	13.5	9.62	5.5
30	34/M	0.59	5.68	3.2	99.5	86.5	2.2	2	4.2	2.04	2.58	4.62	20.8	13.1	9.12	7.7	20	12.8	8.25	7.2
31	36/F	0.4	6.8	2.06	96.5	97.5	2.05	2.5	4.02	2.15	2.05	3.6	20.5	12.5	9.75	8	21.8	12.3	9.12	9.5
32	27/F	0.69	7.2	2.03	95.5	95.5	1.76	2.1	3.86	2.82	1.48	4.03	20.5	13.5	10	7	20.4	12.3	7.38	8.1
33	48/F	0.87	5.8	3.45	92.5	85.5	1.88	1.77	3.65	2.02	1.95	3.97	20.8	13.4	9.12	7.4	20.4	12.9	8.5	7.5
34	55/F	1.33	6.2	2.49	97	93.5	2.57	1.53	4.1	2.13	2.14	4.27	20.6	13.3	9	7.3	20.8	13	6.75	7.8
35	44/F	1.6	9.8	2.35	96.5	96.5	1.62	1.66	3.28	2.3	1.62	3.92	20	13.5	9.62	6.5	20.3	13.6	9.62	6.7
36	39/F	1.67	7.28	3.8	95	98	1.1	1.52	4.62	1.6	1.74	4.34	22	15.4	10.9	6.6	23.4	14.4	9.12	9
37	17/F	2	9.6	2.19	99	94	2.92	1.5	4.42	2.2	1.3	3.5	20	13.3	9.5	6.7	19.9	13	7.62	6.9
38	24/F	0.9	8.2	2.83	96	95.5	1.85	1.95	3.8	1.72	2.18	3.9	20.1	14	9.5	6.1	22.9	13.9	9.12	9
39	64/F	5.6	8.6	3.8	96	91.5	2.62	1.3	3.92	1.45	2.2	3.65	19.5	13.8	7.88	5.7	21	12.3	8.62	8.7
40	29/M	1.66	7.41	4.3	101	102	2.67	1.87	4.54	1.82	2.52	4.34	22.6	13.1	10.3	9.5	22.9	16.5	10	6.4

ELECTROPHYSIOLOGICAL PARAMETERS AND THYROID PROFILE - HYPOTHYROID PATIENTS

s.no	AGE/ SEX	T3 ng/dl	T4 µg/dl	TSH mIU/l	VEP P_{100} LATENCY ms		BAEP LT (ms)			BAEP RT (ms)			SSEP LT (ms)				SSEP RT (ms)			
					LT	RT	I-III	III-V	I-V	I-III	III-V	I-V	N-20	N-13	N9	CCT	N20	N13	N9	CCT
1	22/F	0.14	3.2	9.3	111	107	2.78	2.98	5.7	3.14	2.6	5.74	23.4	14.1	10	9.3	25.5	14.3	9.12	11.2
2	50/F	0.12	2.4	10.2	104	104	2.12	1.95	4.07	2.79	3.28	5.07	27.9	15.3	10.4	12.6	26.4	16.1	9.75	10.3
3	21/F	0.11	2	10.5	110	103	3.22	3.12	6.34	3.87	2.93	6.8	24.9	13.1	10.8	11.8	23.8	15	9.38	8.8
4	26/F	0.18	2.3	6.5	107	107	3	3.04	6.04	3.55	1.62	5.17	23.5	16.8	9.5	6.7	23.8	15.6	9.38	8.2
5	34/M	0.12	3.6	5.4	103	101	3.15	2.32	5.47	3.1	2.52	5.62	24.3	14.1	8	10.2	25.9	15.9	8.75	10
6	30/F	0.08	1.2	8	104	103	2	2.47	4.47	2.8	2.58	5.38	27.9	17.9	10	10	25.8	15	9.75	10.8
7	54/M	0.09	2.28	12	104	103	2.63	2.64	5.27	3.57	1.75	5.32	23.3	14.4	8.62	8.9	25.5	15	8.12	10.5
8	25/F	0.48	2.5	5.8	103	100	2.75	2.5	5.25	3.1	2.55	5.65	24.1	16.6	10.9	7.5	25.9	16.5	8.75	9.4
9	39/F	0.13	1.2	7.46	110	108	2.37	2.03	4.4	2.15	2.3	4.45	21.9	13.3	10	8.6	23.6	14.6	10.5	9
10	45/F	0.67	2.6	5.42	114	112	3.12	1.33	4.45	2.92	1.68	4.6	24.5	16.1	10.4	8.4	27.3	14.8	9.12	12.5
11	50/F	0.13	2.6	8	107	110	1.8	3.04	4.84	2.45	2.52	4.97	27.4	17.8	10.4	9.6	23.8	14.6	10	9.2
12	55/F	0.09	0.68	6.4	93	90	2.58	3.1	5.68	3.9	1.85	5.75	23.8	14.5	9.38	9.3	24.1	13.8	10.4	10.3
13	40/F	0.1	3.97	6.5	104	105	3.35	2.53	4.88	3.43	2.67	5.1	26.6	16.1	10	10.5	23.8	14	10.9	9.8
14	42/F	0.22	3.62	5.02	97	96	3.07	1.87	4.94	1.73	2.6	4.33	23.6	15.5	10.8	8.1	24	13.5	11	10.5
15	27/F	0.23	3.12	7.22	105	106	2.63	2	4.63	2.14	2.63	4.77	26.5	19.8	11.6	4.7	26.9	16.3	10.9	10.6
16	45/F	0.19	2.11	6.51	111	108	2.57	2.23	4.8	2.81	1.85	4.66	24.9	14	10.6	10.9	23.1	14	10.9	9.1
17	17/F	0.8	3.3	5.2	102	103	2.32	2.18	4.5	2.47	2.65	4.12	29.1	13.3	9.75	5.8	25.5	13.9	9	11.6
18	32/F	0.82	3.2	5.56	107	109	3.3	2.3	5.6	3.05	2.55	5.6	26.6	16.1	9	10.5	28.8	16.8	10.8	12
19	33/F	0.04	1.8	8.79	97	97	3.23	1.85	5.08	1.63	3.15	4.78	20.6	13.9	8.75	6.7	20.9	14.1	10.6	6.8
20	50/f	0.2	2.2	19.4	97	97.5	2.38	1.88	4.26	3.04	2.86	5.9	25.5	17.4	11.1	8.1	23.6	14.8	9.12	8.8

ELECTROPHYSIOLOGICAL PARAMETERS AND THYROID PROFILE - HYPOTHYROID PATIENTS

s.no	AGE/ SEX	T3 ng/dl	T4 µg/dl	TSH mIU/l	VEP P_{100} LATENCY ms		BAEP LT (ms)			BAEP RT (ms)			SSEP LT (ms)				SSEP RT (ms)			
					LT	RT	I-III	III-V	I-V	I-III	III-V	I-V	N-20	N-13	N9	CCT	N20	N13	N9	CCT
21	64/M	0.14	1.2	14.2	94	94.5	2.3	1.75	4.05	2.07	1.98	4.05	25	17.8	11	7.2	28.5	13.8	11.1	4.7
22	34/F	0.23	2	9.4	100	100	3.32	2.4	4.72	2.75	2.2	4.95	22.6	15.6	9.38	7	23.6	15.8	9.12	7.8
23	43/F	0.3	3.6	5.5	110	116	1.96	2	4.96	2.03	1.27	4.3	21.4	15	9	6.4	20	12.4	9.38	7.6
24	40/F	0.12	2.2	20.2	103	114	2.94	1.6	4.54	2.5	2.1	4.6	22.4	15.3	10.9	7.1	23.1	17	11.6	6.1
25	49/F	0.24	3.1	7.8	97.5	98	2.06	1.92	4.98	2.28	3.2	5.48	23.5	15.5	9	8	24.9	14.5	10.1	10.4
26	35/F	1.2	2.9	6.2	103	105	2.12	2.3	4.42	2.3	3	5.3	23.4	17.4	10	6	24.4	18.1	8.5	6.3
27	18/F	1.6	2.8	6.8	108	103	1.7	2.4	4.1	2.33	1.5	3.83	25.9	14.8	9	9.1	21.4	15.9	10.9	5.5
28	45/F	1.08	2.3	8.69	100	101	2.18	1.97	4.15	3.03	1.75	4.78	23.1	16.5	7.38	6.6	22.5	13.4	9.12	9.1
29	50/F	0.98	2.43	6.82	102	102	2.32	2	6.32	2.98	3.09	6.07	23.4	19.5	11.4	3.9	26.9	16.4	10.5	10.5
30	63/F	0.26	1.8	12.5	113	114	2.12	2.8	3.92	1.9	2.82	4.72	21.3	13.8	11.9	7.5	23.1	15.4	10.5	7.7
31	64/F	0.16	1.62	10.2	104	107	2.08	2.8	4.88	2.25	3.12	5.37	20.5	13.8	8.88	6.7	20.1	14.8	11.6	5.3
32	19/F	0.83	2.02	7.91	93	90.5	3.02	2.4	5.42	3.2	2.2	5.4	22.3	14.6	10.6	7.7	26.3	16.3	8.88	10
33	47/F	0.64	2.2	20.2	102	104	2.32	2.2	4.52	1.87	2.28	4.15	23	15.3	10.5	7.7	24.8	16.3	9.62	8.5
34	26/F	0.2	1.6	32	105	102	1.97	2.85	4.82	2.15	1.75	4.9	23.8	15.6	9	8.2	27.1	13.9	8.5	3.2
35	42/F	0.94	2.42	7.2	101	101	2.1	2.92	4.02	2.1	2.38	4.48	28.9	14.1	9.88	14.8	21.6	16.8	10.5	4.8
36	40/F	0.14	1.84	9.4	101	101	3.35	1.88	5.23	2.77	1.76	4.53	24.9	15.9	10.6	9	23.9	13.1	8.38	10.8
37	50/M	0.56	1.89	11.2	104	102	2.25	1.7	3.95	2.82	1.4	4.22	24.5	15.6	8.12	8.9	24.3	14	8.38	10.3
38	41/M	0.32	2.2	8.4	111	110	2.83	2.35	4.18	2.3	1.85	4.15	22.8	13	8	9.8	23	13.3	10.3	9.7
39	45/M	0.43	3.2	7.2	111	107	1.93	2.27	4.2	1.45	2.2	4.65	23.8	14.3	9.62	9.5	25.3	14.6	9.25	10.7
40	34/M	0.16	2.4	12.6	101	115	2.52	2.75	5.27	2.18	2.37	4.55	25.9	13.5	10.8	12.4	22.6	14.6	9.62	8